The genetic etiology of cannabis use

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ABSTRACT

Behavior Genetics Association 41st Annual Meeting Abstracts

CNR1, physical abuse and anhedonia: The role of the endocannabinoid system in stress adaptation and mood

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Endocannabinoids, primarily, *N*-arachidonoylethanolamine (anadamide) and 2-arachidonoylglycerol (2-AG) are naturally occurring molecules that have anxiolytic, analgesic and anti-depressant effects. Their influence is partly mediated by the CB1 receptors to which they bind. Recent studies have found that rodents with deficiencies in CB1 receptor activity show anhedonia and depressed mood. In addition, there is accumulating evidence that persistent stress directly contributes to differential fluctuations in anadamide and 2-AG. In rodents experiencing repeated stress exposure, decline in anadamide can modify corticosteroid levels, indicating the endocannabinoid signaling may be critical in adaptation to stress. While the theories linking endocannabinoids to stress adaptation and mood have been validated in rodent models, there are no human studies that clearly demonstrate the nature of this relationship. We examined whether the synonymous SNP, rs1049353, in CNR1 interacted with childhood trauma (physical or sexual abuse) to predict aspects of low mood. In a sample of female twins aged 18–28 years ($N = 1140$), a significant interaction between rs1049353 and childhood physical (but not sexual) abuse was associated with self-reported anhedonia (but not depressed mood). The effect was replicated in an independent sample of 1933 heroin dependent cases and neighborhood controls. In both studies, there was a strong main effect of physical abuse [O.R. > 3.0] but not of genotype. After accounting for the potent main risk influence of physical abuse, the absence of the minor (A) allele was associated with significantly increased rates of anhedonia (58%) in individuals who also experienced childhood physical abuse. While our results are highly consistent with the rodent literature, we cannot determine (as the function of rs1049353 is not well understood) whether this interaction reflects the action of the minor allele in buffering the effects of abuse on anhedonia or whether the presence of the major allele confers risk for anhedonia in the presence of abuse.

Genome wars, obesity, and addiction: Why Dobzhansky would have loved the modern era

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Julia Grant; Washington University School of Medicine
Christina Lessov-Schlaggar; Washington University School of Medicine
Alexis Duncan; Washington University in St. Louis
Arpana Agrawal; Washington University in St. Louis

As Dr. Heath was unable to present his Dobzhansky lecture, his colleagues presented research ideas inspired by Dr. Heath. Dr. Knopik introduced Dr. Heath to the attendees, discussing his renowned generosity and ability to successfully transition his junior colleagues to independently funded investigators. She shared her early experiences with Dr. Heath and recapitulated some of the key lessons she learned from him that continue to influence her case-crossover study of smoking during pregnancy. Dr. Julia Grant was mentored by Dr. Heath as a postdoctoral trainee and subsequently transitioned to becoming a long-term colleague. She presented on their shared interest and research into genetic models of assortative mating for alcoholism that was based on the early models for the detection of primary assortment and reciprocal marital interaction developed by Dr. Heath. Dr. Lessov-Schlaggar presented an overview of the Missouri Adolescent Female Twin Study (MOAFTS), a longitudinal cohort of female twins who are now in their seventh wave of data collection. She described the enormous utility of this sample and the manner in which Dr. Heath has successfully invited MOAFTS participants to contribute to ongoing studies, such as the gut microbiome project. Dr. Duncan presented an overview of her exciting work with Dr. Heath on the gut micorbiome project as well as her experiences as

a postdoctoral scientist with Dr. Heath, which served as her introduction to the twin method. The session was concluded with a review of some of Dr. Heath's seminal publications in the area of addiction genetics by Dr. Agrawal and thoughts on avenues for future research.

Age at regular drinking and alcohol dependence: Gene-environment interplay in the study of addictions: Gene and environment

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Early onset of alcohol use has been linked to increased likelihood of alcohol dependence. Twin studies suggest that early onset alcohol use is heritable and that genetic influences on early onset alcohol use overlap with those on alcohol dependence. In addition to the evidence for correlated vulnerabilities to early onset use and later dependence, studies show that early onset alcohol use may also have an environmental influence on alcohol dependence. In particular, multiple twin studies have suggested that onset of alcohol use may facilitate the unveiling of genetic vulnerability to alcohol dependence via gene x environment interactions. There is also preliminary evidence that this interaction persists after accounting for gene-environment correlation. This is the first study that proposes to examine these hypotheses using genomewide association data. Using data from SAGE, we will examine (a) SNPs associated with age at regular alcohol use, coded as early (less than 18 years), or later; (b) whether the effect of SNPs associated with alcohol dependence is modified by early age at regular alcohol use. SNPs associated with early age at regular drink were significant at 1.3E−6 and higher and included multiple SNPs in GPC5, GABRG3 and CDH12. Early age at regular drink was a potent covariate of alcohol dependence (O.R. 7.4 [95% C.I. 6.3–8.8]). Interactions between early age at regular drink and additively coded genotype were significant at $p > 1E{-}7$ however none of the top SNPs were those previously reported by Bierut and colleagues nor were they in candidate genes previously implicated in the etiology of alcoholism. Analyses conducted in the subset of early drinkers showed similar results with no evidence for the main effects of the SNPs involved in interactions on early age at regular drinking (Rge).

Moderation of the efficacy of an attention bias modification program for social phobia by aggregate genetic risk in serotonergic genes

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We conducted a randomized, double-blind placebo-controlled trial to examine the efficacy of an attention training procedure in reducing symptoms of social anxiety in individuals diagnosed with Generalized Social Phobia (GSP). Attention training comprised a probe detection task where pictures of faces with either a threatening or neutral emotional expression cued different locations on the computer screen. In the Attention Modification Program (AMP), participants responded to a probe that always followed neutral faces when paired with a threatening face, thereby directing attention away from threat. In the Attention Control Condition (ACC), the probe appeared with equal frequency in the position of the threat and neutral faces. We also examined whether specific genetic influences would moderate the impact of AMP. Specifically, using an aggregate genetic risk score (AGRS) approach, we examined variation in two genes that influence serotonergic activity—5-HTTLPR and TPH2. Conceptualizing AMP as an environmental influence and AGRS as reflecting genetic plasticity within a model of differential susceptibility to environmental influence, we predicted that patients scoring higher on this AGRS would exhibit greater benefit from AMP than patients with lower AGRS scores.

Supporting this hypothesis, preliminary results suggest that there was an interaction of group (AMP vs. ACC) and AGRS scores such that patients with low AGRS scores responded similarly to the two computer programs. However, among those with high AGRS scores, there was a nearly threefold response in the AMP group compared to the ACC group. No such results were obtained when using only the 5-HTTLPR gene classification. These results suggest that a computerized attention training procedures may be beneficial for treating social phobia and highlight the need to use more sensitive measure of genetic vulnerability including the aggregate genetic risk score approach.

Genetic stability and change of cognitive abilities in adulthood: A 7-year longitudinal study

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Genetic influences on cognitive development in adulthood have not been well-investigated compared to in childhood and old age. The current study examined genetic and environmental stability and change of verbal and spatial abilities during adolescence and young adulthood over about seven-year interval. Longitudinal twin data from Keio Twin Project, including two verbal (sentence completion and rearrangement of words) and two spatial (paper folding and mental rotation) subtasks, were available. Mean ages (SD) at time 1 (1998/1999) and at time 2 (2005/2006) were 20.0 (3.3), and 25.1 (4.3) respectively (mean age difference was 7.3 (.5). Phenotypic stabilities were substantially high ($r = .51$–$.71$ for subtask scores and $r = .81$ for total scores). Cholesky analyses indicated that those phenotypic stabilities were mainly mediated by genetic factors and significant novel genetic contribution emerged for rearrangement of words. Significant increase of genetic contribution was observed for verbal and total scores.

Environmental factors in subjective wellbeing: Evidence from discordant and concordant monozygotic twins

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Twin and family studies revealed that 40–50% of the variance in SWB is explained by genetic factors (Bartels, M., and Boomsma, D.I.

(2009). Behar Genet, 39(6), 605–615), while the remaining variance is accounted for by nonshared environmental factors. A very powerful design to identify environmental risk factors is the discordant MZ twin design. Because MZ twins share nearly all of their genetic material, discordance in their behavior will mainly reflect the effects of differential exposure to environmental risk and protective factors. A population based sample of 14-year-old identical twins ($n = 800$ twin pairs, 50% male) will be divided into three groups: (1) concordant high scoring twin pairs (2) discordant scoring twins pairs, where one of the twin pairs scores average or higher on wellbeing, while the other scores significantly below average; (3) concordant low scoring pairs.

Differences within pairs and between pairs of the three distinct groups will be investigated for the prospective longitudinally collected variables of the Young Netherlands Twin Register, such as perinatal circumstances, life events, use of medication (e.g. anesthetics), life style choices (e.g. physical activity, leisure time, religiosity, substance use), and education.

A genome-wide association study for subjective wellbeing

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Information on causes of individual differences in subjective wellbeing (SWB) can provide additional insights into the causes of variation in psychopathology and provide handles for prevention and treatment of mental health problems. To this end knowledge on the causes of individual differences in subjective wellbeing and the factors that jeopardize or promote wellbeing is crucial. Twin and family studies revealed that 40–50% of the variance in SWB is explained by genetic factors (Bartels, M., and Boomsma, D.I. (2009). Behar Genet, 39(6), 605–615).

To our knowledge, no candidate gene studies have been performed for SWB, so no replicable findings have yet emerged to explain the heritability in terms of measured genetic variants. To identify specific genomic regions of interest for variation in SWB an international consortium (QENEQOL) has been established. As a first step, we present the Genome-Wide Association analysis that will be conducted in Dutch samples. Genome-wide SNP data and phenotypic information on SWB are available for 8321 individuals from the Netherlands Twin Register (NTR).

Altruism or altruisms? Kindness across sex and in three social domains

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Prosocial behaviour is heritable. Here we explore the origins of prosociality in narrower facets of behaviour. In particular, we focus on the role of common and specific mechanisms in behavior related to civic duty, work-role specialisation, and concern for the welfare of others. In 958 adult twin-pairs, multivariate modelling indicated the existence of a general prosocial obligation factor in both sexes, with stronger genetic effects in females than males. At the domain-specific level, modest genetic effects were observed in females for civic and work obligations, with shared-environment effects influencing welfare obligations. In males, genetic influences were observed for welfare obligation, with unique environments affecting work and civic duty. The implications of these data for the evolution of altruism and group behaviour are discussed.

Implications of phenotype-environment correlations in developmental models

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Gene-environment (rGE) correlation can exist both within and between families (Scarr &435). Between families, accumulating rGE has been used to explain dramatic changes in phenotypic means over time. The Dickens-Flynn model (2001, Psych. Rev., 108, 346–369), for example, suggests that small genetically-driven changes in phenotype can lead to subsequent reallocation of environmental resources. This process sets up reciprocal feedback between phenotype and environment, producing increasing amounts of rGE, and under the right circumstances, dramatic changes in the mean of phenotypes that are highly heritable cross-sectionally. We propose that similar processes operate within twin and sibling pairs. Especially in DZ twins and siblings, small differences in genotype can become associated with reallocations of environmental resources, and therefore rGE within families. Such processes can lead to relatively high degrees of stability of pair differences over time, differences between the within pair developmental trajectories of MZ and DZ twins, and misspecification of typical longitudinal twin models that don't include appropriate rGE.

We conducted a two-part analysis to evaluate the hypothesis that developmental twin models that include rGE fit better than models that do not include rGE. First, we simulated data that explicitly model rGE effects at different values. We then fit traditional longitudinal twin models to these data (e.g., saturated Choleksy ACE models; Bartels et al., 2004, Dev. Psych., 40, 852–867) to evaluate the misspecification of models that do not include rGE. Second, using longitudinal cognitive ability data from a subsample of the Minnesota Center for Twin and Family Research study (Iacono, McGue, & Krueger, 2006, Twin Res. & Hum. Gen., 9, 978–984), we compared the fit of traditional developmental ACE models to models that include rGE. Implications for the differential development of MZ and DZ twins and alternative approaches to longitudinal twin analysis are considered.

Genetic and environmental influences on associations between child–family relationship subsystems across time

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Parent–child and sibling relationships are theoretically linked as subsystems that transact across development as part of a higher-order

family system (Cox & Paley, 1997). Understanding the relationship between these two family subsystems, as children develop, is vital for family interventions aimed at promoting more adaptive family systems.

This study extends prior research by using a common pathway model to investigate how genetic and environmental factors influence the communalities between mother–child, father-child, and sibling relationships characterized by conflict/negativity and warmth/positivity in middle adolescence and early young adulthood.

Participants include siblings ($n = 708$, 49% female) assessed in middle adolescence (ages: 10–18) and young adulthood (ages: 20–35). Sibling pairs varied in degree of genetic similarity, and include monozygotic twins, dizygotic twins, full siblings from non-divorced and step families, half siblings, and unrelated siblings.

Best-fitting common pathway model results using OpenMx (Boker, Neale, et al., 2011) suggest extremely strong shared (c2 = .85, 95% CI = [.73–.98]) and weak unique environmental (e2 = .15, 95% CI = [.04–.27]) influences on the relationship between the parenting and sibling subsystems in adolescence This is in stark contrast with moderate genetic influence, originating in the child (a2 = .38, 95% CI = [.23–.51]) and unique environmental (e2 = .62, 95% CI = [.49–.77]) influences on the association of conflict in the two subsystems. Patterns appear similar in early young adulthood but power is limited due to sample size. Findings suggest communalities in warm and conflictual family relationships are differentially influenced by genetic and environmental factors and have direct relevance for the targeting of family systems interventions.

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Moving beyond a single SNP: Aggregate genetic risk score and epistatic associations with processing of emotional information

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A number of studies have examined the association between a specific single nucleotide polymorphism (SNP) and intermediate phenotypes thought to increase risk for psychopathology, such as biased attention for emotion stimuli. Although promising, it does not account for the fact that multiple genes likely contribute to complex phenotypes such as biased processing of emotion stimuli. Thus, we examined whether two alternatives to a single SNP approach, aggregate genetic risk score (AGRS) and genetic epistasis, predicted individual differences in the cognitive processing of emotional stimuli among 183 healthy adult participants. For our AGRS analyses, we counted number of risk alleles in four polymorphisms known to influence prefrontal cortex function (i.e., COMT, DRD4, HOMER1, BDNF). This AGRS significantly predicted difficulty shifting attention away from task stimuli (i.e., cue validity x AGRS interaction; $F(1, 1261) = 10.89$, $p = .001$), but it did not interact with stimuli valence. Number of risk alleles was associated with longer time to disengage attention from task stimuli. For epistatic analyses, we examined interactions between the 5-HTTLPR and TPH2 genotypes, as both influence limbic system response to emotional stimuli. We found a significant epistatic relationship between the 5-HTTLPR and TPH2 polymorphisms (i.e., cue validity × emotion stimuli × 5-HTTLPR genotype × TPH2 genotype interaction; $F(12, 1219) = 1.78$, $p = .046$). Individuals with the short 5-HTTLPR allele and the T variant of the TPH2 polymorphism had more difficulty disengaging attention from negative emotion stimuli. Thus, several polymorphisms previously shown to influence prefrontal function appear to also influence difficulty with shifting attention from stimuli. Further, two genes previously shown to influence emotion processing confer difficulty disengaging attention from negative stimuli. This work highlights two alternative approaches to a single SNP framework and provides new insight into how multiple genes might contribute to complex phenotypes that confer vulnerability to psychopathology.

Genotype and ADHD symptoms interact to predict adolescents' early smoking experiences in an epidemiological sample

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Introduction: The valence (positive or negative) of the initial reaction to cigarette smoking predicts later regular smoking. Symptoms of attention-deficit hyperactivity disorder (ADHD) increase smoking risk and may moderate the relationship between genotype and smoking. We conducted an exploratory study to assess whether ADHD symptoms interact with genotype to predict the valence of self-reported initial reactions to smoking. *Methods*: Participants were a subsample of 1,900 unrelated individuals with genotype data drawn from the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative sample of adolescents followed from 1995 to 2002. Linear regression was used to examine relationships among self-reported ADHD symptoms, genotype, and self-reported initial reaction to cigarettes (9 items reflecting pleasant or unpleasant reactions). *Results*: Polymorphisms in the DRD2 gene, SLC6A4 gene, and, among males, the MAOA gene interacted with retrospective reports of ADHD symptoms in predicting pleasant initial reaction to cigarettes. Polymorphisms in the CYP2A6 gene, and, among females, the MAOA gene interacted with retrospective reports of ADHD symptoms in predicting unpleasant initial reaction to cigarettes. No main effect for any of these polymorphisms was observed nor were any interactions with DRD4 and DAT genes. *Conclusions*: These findings suggest that genotypes associated with monoamine neurotransmission interact with ADHD symptoms to influence initial reactions to cigarette smoking. Given that initial reactions to cigarettes also predict lifetime smoking, these results add to a growing body of literature that suggests ADHD symptoms increase risk for smoking and should be accounted for in genetic studies of smoking.

Genetic variation and impulsivity: The association between cannabinoid receptor 1 gene (CNR1) and components of impulsivity in young adult marijuana users

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Objective: Marijuana use has been associated with both risk-taking and impulsivity. Despite findings that candidate genes in the endocannabinoid system are associated with marijuana use (i.e. Hopfer et al., 2006) and substance use more broadly (i.e. Hutchison et al., 2008), few studies have examined the role of genetic variation on measures of impulsivity. This study examined the genetic association between variation in the cannabinoid receptor 1 (CNR1) gene and three measures thought to represent different components of impulsivity, including a self-report personality questionnaire (trait-based impulsivity) and two delay discounting tasks (behavioral impulsivity). *Method*: As part of the baseline assessment of a larger study of marijuana's acute effects (Metrik et al., 2011), 150 young adult weekly marijuana users (Mean age = 21.6, SD = 3.2) provided a DNA sample and completed the Barratt Impulsiveness Scale (BIS-11), the Experiential Delay Discounting Task (EDT), and the Delay Discounting Questionnaire (DDQ). Three SNPs in the CNR1 gene were genotyped: rs806368, rs1049353, rs2023239. Associations between variation in the CNR1 gene and baseline impulsivity variables were examined using PLINK (Purcell et al., 2007).
Results: Analyses identified significant associations between CNR1 SNP variation and each of the impulsivity measures (R^2 range from .025–.039; *p* values range from .016–.055).
Conclusion: These results provide initial evidence of association between CNR1 variation and impulsivity in marijuana users as measured by both trait-based personality scales and real-time behavioral tasks. Further, these preliminary findings add to a growing body of literature suggesting that CNR1 variation is associated with substance use and impulsivity-related phenotypes.

Empirical significance for low-frequency common variants

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Genome-wide association studies (GWAS) have uncovered hundreds of loci relevant to common/complex disease, but are limited to studying SNPs with minor allele frequency of at least 1–5%. Despite incomplete coverage in GWAS, a number of rare variants have been implicated in complex disease [1, 2]. It is well-established that classical association tests are inappropriate for analysis of less-common variation, given a tendency of Pearson's χ^2 to overestimate significance when observed counts are small. To avoid systemic accruement of false-positive findings, Yates' correction is often applied but is itself prone to returning somewhat deflated probability estimates [3]. Given that the field has adopted a genome-wide significance threshold (5e−8), the accuracy of extreme *p*-values is of essential to detection and replication of disease-SNP associations. To enhance our understanding of the asymptotic properties of traditional tests, we conducted a range of null simulations of the allelic χ^2, Armitage trend, and Wald tests. As our goal was to assess asymptotic behavior, we chose to conduct a large number of simulations (1B) for each scenario. Initially, we considered a 1% MAF SNP in 2,000 cases/controls, assigning individual genotypes randomly and thereby allowing for sampling variance. We further constrained the tests' behavior by fixing the total number of minor alleles. To determine whether sample-size matters, we compared models featuring 40 copies in 2,000 or 10,000 cases/controls. We also considered 20 and 80 copies in 10,000 cases/controls. To quantify deviations from expected behavior, we tabulated significant differences for various α-levels and compared these to the theoretical χ^2(1df). We observed marked deviations from expected behavior for each test, with fewer minor alleles corresponding to a greater degree of deflation. The effect becomes more pronounced at progressively smaller α and considerably more so for the Wald Test. Additionally, we consider Fisher's Exact Test and discuss its suitability when classical tests prove inadequate.

An examination of the developmental pathways model of oppositional defiant disorder in a genetically informative sample

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Recently, Loeber and colleagues presented a new developmental pathway model for Oppositional Defiant Disorder (ODD) that examined both behavioral and emotional components of the disorder (J.B. Burke & R. Loeber, 2010, Clin Psychol Sci Pract, 17, 319–326; R. Loeber & J.D. Burke, 2011, J Res Adolescence, 21, 34–46). According to the model, there are two components of ODD symptoms. The affective component consists of ODD symptoms "touchy", "spiteful", "angry", and "vindictive", and is more likely to lead to future internalizing disorders, whereas the behavioral component consists of ODD symptoms "arguing", "being defiant", and "losing one's temper", and is more likely to lead to future CD. Results supporting the distinction between the affective and behavioral dimensions of ODD and their association with depression vs. CD have been found in prior research (J.D. Burke, R. Loeber, B.B. Lahey, & P.J. Rathouz, 2005, J Child Psychol Psychiatry, 46, 1200–1210). The current longitudinal and genetically informative sample consisted of twin pairs from the Longitudinal Twin Study and the Colorado Twin Study (S.A. Rhea, A.A. Gross, B.C. Haberstick, & R.P. Corley, 2006, Twin Res Hum Genet, 9, 941–949). The Diagnostic Interview Schedule for Children (DISC-IV) was used to assess psychopathology between the age of 12–17 and a second time 5 years later. We attempted to replicate the distinction between the affective and behavioral dimensions in ODD, and examined whether the affective dimension was associated with the development of depression, whereas the behavioral dimension was associated with the development of CD later in adolescence. The results of the factor analyses examining the ODD symptoms did not support a distinction between negative affect and oppositional behavior, and the results from the present study did not support the developmental pathway model.

Qualitative and quantitative sex differences in genetic architecture for human phenotypes

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Large genome-wide association (GWA) studies of complex phenotypes frequently consider the effect of genetic variants separately in men and women, hypothesizing that the effect of a particular allele may be different across sex. We tested for quantitative and qualitative sex differences in genetic architecture for a broad range phenotypes using data from same-sex and opposite-sex twin pairs from the Netherlands Twin Register (NTR).

We present results for data collected across the life span (age 3 through 65) for substance use and abuse, personality and psychiatric outcomes, cognition, migraine, exercise behavior, body mass index, migraine and cardiovascular traits. Statistical analyses were performed with structural equation modeling as implemented in the software package Mx. There is not much evidence for genotype x sex interaction, with exceptions for, for example, some of the cardiovascular risk factors. For a number of traits, outcomes from the twin based analyses will be compared to GWA studies that tested for genetic association separately in men and women.

The traditional moral virtues triad (authoritarianism, religiousness & conservatism) and the role of obedience

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Religiousness and its' strongly associated traits of Authoritarianism and Conservatism form a cluster called the Traditional Moral Values Triad (TMVT). These traits have been denigrated by academics since their condemnation by Marx, Freud and Nietzche, early scholars in the social sciences whose influence continues to be pervasive. The possible positive attributes of these traits are seldom discussed. I provide evidence that "Obedience to authority" is the construct that ties the TMVT together and argue that the higher order construct implied by the correlations should be called Traditionalism. Religiousness, rather than being an opiate of the masses (Marx) or a universal neurosis (Freud) is in part one manifestation of an underling human evolutionary adaptation to sociality, namely the propensity to obey authority. Herbert Simon's theory of the evolution of docility is revised and meshed with Johnathan Haidt's model of the evolution of morality to illustrate a plausible evolved mechanism underlying the propensity to "Obey Authority".

Genetic and environmental risk modulates links between attention control and socioemotional adjustment

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Genetic risk predicts adjustment difficulties in children. Yet, it is unclear whether self-regulation modulates risk for maladjustment. In the current study, we examined how attention control moderates associations between early genetic and environmental risk and children's longitudinal adjustment.

The sample included participants in the Early Growth and Development Study ($N = 361$), a study of adopted children, adoptive parents (AP) and birth parents (BP). Genetic risk for anxiety was defined as BP scores on the Beck Anxiety Inventory (BAI) when children were 9 months of age. Environmental risk for anxiety was defined as AP scores on the BAI when children were 9 months of age. Attention control was scored as children's ability to shift attention away from a frustrating event (barrier task) during a home visit when children were 9 months old. APs reported on adjustment using the CBCL Total Problems scale at 18 and 27 months.

We found a marginally significant 3-way interaction among BP anxiety, AP anxiety, and attention control predicting total behavior problems at age 18 months ($\beta = .12$, $t = 1.92$, $p < .10$). For children with BPs who were anxious but APs who were nonanxious, greater attention control at 9 months was associated with fewer total problems at 18 months ($\beta = -.28$, $t = -2.66$, $p < .01$). Greater AP anxiety predicted more total problems.

We also found a significant 3-way interaction among BP anxiety, AP anxiety, and attention control predicting total behavior problems at age 27 months ($\beta = .16$, $t = 2.60$, $p = .01$). Again, for children with BPs who were anxious but APs who were nonanxious, greater attention control at 9 months was associated with fewer total problems at 18 months ($\beta = -.25$, $t = -2.16$, $p < .05$). Greater AP anxiety was directly associated with more total problems. Findings support the idea that parents scaffold emotion regulation for their children and that individual differences exist in susceptibility to environmental influences on adjustment.

Are there really etiological differences between aggressive and non-aggressive antisocial behavior? A nuclear twin family study extension

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A prior meta-analysis of 103 twin and adoption studies revealed evidence of significant etiological distinctions between aggressive (AGG) and non-aggressive rule-breaking (RB) forms of antisocial behavior (Burt, 2009). AGG was observed to be highly heritable (65%), with little role for the shared environment. By contrast, while genetic influences also contributed to RB (48%), there was an important role for shared environmental effects as well (18%). Although these results are indicative of etiological distinctions between AGG and RB, this support is tempered by some key limitations. In particular, the vast majority of behavioral genetic studies on this topic (and thus, the research included in the Burt (2009) meta-analysis) made use of the classical twin design. This more or less exclusive use of the classical twin design is problematic, since it is known to produce biased estimates of genetic and environmental parameter estimates under several conditions (e.g., in the presence of assortative mating, when both dominant and shared environmental effects influence the phenotype, etc.; Keller et al., 2010). We thus sought to constructively replicate and extend the results of Burt (2009) using a nuclear twin family design, which circumvents many of these overly stringent assumptions. The sample will consist of 312 twin pairs and their parents participating in the Twin Study of Emotional and Behavioral Development—Child (TBED-C), a study within the Michigan State University Twin Registry (MSUTR).

Parents report on their own AGG and RB, and on the AGG and RB of each of their twins. Results will be discussed in light of both prior results for AGG and RB, and biases stemming from the field's exclusive focus on the classical twin design.

Variants in the serotonin transporter gene mediate risk and onset of depression following traumatic brain injury

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Genetic variation in the serotonin transporter (5-HTT) promoter region has been associated with risk for depression, especially after stressful life events. In this study, genetic variants of the polymorphic region 5-HTTLPR, including a single nucleotide polymorphism (SNP) rs25531 and a length variation, and the variable number of tandem repeats (VNTR) in Intron 2 were studied in association with development of depression in 78 persons with moderate to severe traumatic brain injury (TBI). All patients were genotyped, and depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9) at 6 and 12 months post-injury. Of these participants, 21 (30.9%) were depressed at 6 months and 15 (25.4%) were depressed at 12 months. Results at 6 months indicate an early protective role for the S allele, contrary to idiopathic depression literature. At 12 months, the LG allele was protective. Expression level analysis using a literature based triallelic paradigm (L with A/G designation and S) was not significant, due to differences in the LG and S allele alleles association with depression at 6 months. This suggests they may be regulated differently under the neurobiological stress of TBI. The S and 12 allele of the VNTR seem to be protective against all subsets of post-traumatic depression. Half of LG carriers never became depressed and the other 50% experiencing transient depression with recovery by 12 months. Our study is unique in examining depression across recovery, dissecting differences between transient depression, persistent depression and late-onset depression. The implications of this study warrant further investigation of the role of genetic variation in post-TBI depression, especially across recovery. This study may provide a basis for earlier detection and intervention for individuals at risk for post-traumatic depression, allowing for preemptive treatment to minimize the effects of depression on recovery in these patients.

A developmental twin study of attention problem: Evidence for genetic stability and innovation

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Background: The high heritability of Attention Problem (AP) and other ADHD-related phenotypes has been repeatedly demonstrated, but few studies have tested in a developmental genetically sensitive design the stability and change of genetic influences on AP from childhood to young adulthood.

Method: 1480 twin pairs from the Swedish Twin Study of Child and Adolescent Development (TCHAD) were prospectively followed from childhood to young adulthood. Symptoms of attention problem were obtained at ages 8–9, 13–14, 16–17 and 19–20 both by parent and self ratings. Analysis was conducted using longitudinal structural equation modeling with multiple informants.

Results: Genetic effects operating at age 8–9 continued to impact at following time points, explaining 41, 34, and 24% of the total variance at ages 13–14, 16–17 and 19–20. Moreover, new sets of genetic risk factors emerged at ages 13–14, 16–17 and 19–20. The best-fitting model revealed high heritability of AP as indexed by parent and self ratings from childhood to early-adulthood ($h2 = 0.77$–0.82). Parent ratings were a better index of AP than self ratings. There was no evidence of sex differences in the genetic and environmental influences on AP over time.

Conclusion: The individual differences in AP are highly heritable from childhood to young adulthood, and both genetic stability and genetic innovation are present through the development. Longitudinal twin study results may help to identify a refined AP or ADHD phenotype for molecular genetic studies.

Childhood maltreatment moderates heritability of aggression in adults

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The association between childhood maltreatment and aggressive behavior in adults has been widely documented. In addition, a substantial body of work suggests that individual differences in aggressive behavior may be due to an interaction of history of childhood maltreatment with specific genotypes (e.g., MAO-A genotype). However, whether childhood maltreatment alters the genetic and environmental processes underlying adult aggression has not been explored using the twin design. The current study examined this question using a sample of $N = 2093$ same-sex adult twins (71.9% MZ twins; 40.1% males) aged 20–55 from the PennTwins Cohort, a population-based sample of twins born in Pennsylvania between 1959 and 1978. Adult aggression was assessed with the Life History of Aggression questionnaire. Childhood maltreatment was measured using the Childhood Trauma Questionnaire. Participants were divided into three groups based on their levels of childhood maltreatment: a no-maltreatment group ($n = 898$), a low-maltreatment group ($n = 650$), and a moderate/high-maltreatment group ($n = 545$). Multi-group models were fitted for males and females separately to compare genetic and environmental influences on adult aggression across the three maltreatment groups. Results indicated that genetic and non-shared environmental factors, but not shared environmental experiences, accounted for variance in adult aggression for both males and females. Heritability and non-shared environmental effects did not differ across the three maltreatment groups for males ($h2 = .48$; $e2 = .52$). For females, non-shared environmental factors explained more variance in adult aggression for the moderate/high-maltreatment group than for the no- and low-maltreatment groups. There was no difference between groups in the magnitude of genetic factors. However, the between-group differences in non-shared environmental effects resulted in an observed difference in heritability between the moderate/high-maltreatment group ($h2 = .30$) and the other two groups with lower levels of maltreatment ($h2 = .47$). Findings suggest that high-level childhood

maltreatment reduces heritability by amplifying non-shared environmental influences on adult aggression, but only in females.

A longitudinal behavior genetic model for ordered categorical variables

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A developmental behavior genetic model is proposed, for the analysis of longitudinal twin data that is measured by ordered categorical variables. In the proposed model, genetic growth curve model (McArdle, 1986 and McArdle et al., 1998) has been combined with a method of modeling ordered categorical variables.

In order to model repeatedly measured ordered categorical variables, observed categorical variables are assumed to be categorizations of unobserved continuous variables. Proportional changes in response categories across time were captured by growth factors by means of mean and variance changes in underlying continuous variables. These growth factors were decomposed into genetic and environmental components.

The proposed model was tested using the data sets generated from varying conditions. From the analyses of the generated data sets, it was found that model parameters, and relative contributions of genetic and environmental factors to growth factors, were successfully estimated. However, for some parameters, estimates of standard errors were biased and statistical power to detect non-zero parameters was not sufficient.

Increasing sample sizes helped estimations the standard errors, but, for some conditions, the bias still existed in relatively large sample sizes ($n > 10000$). Alternative model specification, which specifies equivalent models without the problematic parameters also helped. However, increasing sample sizes is not always possible and the alternative model specification has limited applications in real data analysis.

Although some irregularities were found, the relative contributions of genetic and environmental components on growth factors were well estimated in all conditions. Given that many psychological measurements collect ordered categorical variables, the ability to incorporate such variables reflects substantial expansion within developmental behavior genetics studies.

Interaction between COMT polymorphism and trauma predicts PTSD symptoms in veterans

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Post-traumatic stress disorder is an anxiety disorder that by definition develops in response to trauma; veterans are a population that is particularly at risk for developing this disorder. A number of studies have implicated various genes as possible risk factors in developing PTSD, including the gene that codes for catechol-O-methyltransferase (COMT). Previous studies have found that different genotypes of a particular functional polymorphism of COMT have differential risk for developing PTSD; specifically, those with two Met alleles (as opposed to two Val alleles or one of each) develop more PTSD symptoms in response to trauma. The current study used data from the Minneapolis VA Medical Center ($n = 238$) to analyze the gene by environment interaction between COMT, exposure to trauma, and development of PTSD symptoms, as defined by the Simms four factor model. All subjects were assessed for exposure to traumatic events both before and during deployment. The interaction between trauma and COMT was a highly significant predictor of the level of PTSD symptoms; those with the heterozygous genotype (Val/Met) experienced significantly fewer symptoms at high levels of trauma compared to those with either homozygous genotype. This relationship held even after taking into account covariance with other risk factors for PTSD, such as negative emotionality, internalizing, and pre-deployment depression.

Risk for suicidal behavior following prenatal maternal stress exposure

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Etiological theories suggest associations between altered early development and later suicidal behavior. Previous research, however, has been unable to provide strong causal evidence regarding risk factors for suicidal behavior. To improve etiological understanding of suicidal behavior, we used a quasi-experimental design—random timing of exposure to stress before, during, and in the first 4 years after pregnancy—to examine early risk factors for suicidal behavior. This allowed for increased control over often unmeasured genetic and environmental factors that may influence suicidal behavior.

Swedish population registers from 1973 to 2009 were linked to form a dataset of 3,118,116 live-born, singleton offspring. Maternal stress was defined as the death of a first degree relative of the mother during pregnancy and 27,710 stress-exposed cases were identified. A total of 29,795 offspring (66% women) engaged in suicidal behavior (i.e. attempted or completed suicide). We used Cox regression to calculate adjusted hazard ratios (aHR) for first suicide behavior. Analyses controlled for offspring sex, parity, and maternal and paternal age at child birth.

The risk for a suicide attempt increased following first year exposure to maternal stress (HR = 1.13, 95% CI, 1.03–1.25). The magnitude of association remained elevated only for the first year exposure period after adjustment for covariates and in sibling comparison analyses (aHR = 1.20, 95% CI, 0.70–2.13). Due to the robust quasi-experimental design, these results suggest that further investigation be made into insult exposure in the first year of life and later suicidal behavior.

Within-person investigations of drinking across weekends and weekdays

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Behavioral genetic studies have consistently shown that drinking volume among adults is influenced by genetic as well as by environment influences. These findings apply to person—level drinking, and as such do not address how drinking and the potency of its genetic and environmental influences may vary by specific contexts. The contexts we consider here are weekends and weekdays. People

generally drink more on weekends than weekdays. Biometric models are applied to weekend and weekday drinking volume outcomes constructed from male and female adults' (Mean Age = 54) day—specific reports of number of drinks drawn from the National Study of Daily Experiences. Available data varied across weekdays and weekends, with 74 and 43 MZ and DZ twins pairs having complete weekday data and 64 and 38 MZ and DZ pairs having complete weekend data. As expected, there was less drinking during the week than on the weekend. Heritability of weekday drinking was estimated to be .46, whereas estimated heritability of weekend drinking was .30.

A within-group design of nontreatment seeking 5-HTTLPR genotyped alcohol-dependent subjects receiving ondansetron and sertraline: Future directions

James Clifford; Brown University

Serotonergic mechanisms are associated with the development of alcohol dependence (AD); however, studies evaluating serotonergic medications have produced conflicting results. The aim of this study was to match and mismatch L/L (associated with early onset alcoholism), and S/S or S/L (associated with late onset alcoholism) genotypes of the serotonin re-uptake transporter (5-HTT) with administration of ondansetron and sertraline in a non-clinical setting.

Fifteen nontreatment seeking alcohol-dependent individuals were randomized to 1 of 2 counterbalanced arms to receive either 200 mg/day of sertraline or 0.5 mg/day of ondansetron for 3 weeks followed by an alcohol self-administration experiment (ASAE), then received placebo for 3 weeks followed by a second ASAE. Participants then received the alternate drug for 3 weeks followed by a third ASAE.

At the first ASAE compared to sertraline, ondansetron significantly improved drinking outcomes for the L/L genotype for the ASAE volume consumed (100% reduction based on between-subjects comparisons, $t = 2.35$), and drinks per drinking day during the 7 days prior to the ASAE (79% reduction, $t = 4.34$). Compared with ondansetron for S/S or S/L genotypes, outcomes at ASAE 1 for sertraline and S/S or S/L genotypes are opposite than hypothesized. Overall, subjects reduced drinking across their participation in the trail, as there appears to be an order effect.

Thus study suggests that ondansetron may reduce alcohol consumption in alcohol-dependent individuals who have the L/L genotype as measured naturalistically and during the ASAE. By contrast there was no support that sertraline reduces alcohol use in individuals who have S/S or S/L genotypes. Evidence in the literature suggests that AD in some individuals may be influenced by a gene by socio-environmental interaction making the pharmacological treatment with serotonergic drugs complex. This study has served as a starting point for future research into treatment seeking individuals.

Serotonin transporter genotype moderates the association between socioeconomic status and anxiety in children

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A variation in the serotonin transporter gene (5-HTTLPR) may moderate the association between stress and depression, such that carriers of at least one low-expressing short or LG allele (s') are only at greater risk under conditions of early or recent stress (A. Caspi et al., 2003, Science, 301, 386–389). We hypothesized that 5-HTTLPR would moderate the association between SES and depression and anxiety in childhood, such that relative to children with the l'/l' genotype, s'/s' homozygotes would have higher symptoms under low SES conditions, with heterozygous children having intermediate symptoms. Participants were 758 twins (50% female), 95% Caucasian, $M = 7.54$ years ($SD = .93$) participating in the Wisconsin Twin Project. Composites were formed from mother and father reports of twin symptoms on the Health and Behavior Questionnaire, Child Depression Inventory, and Diagnostic Interview Schedule IV for Children. SES was a composite of parents' Hollingshead Index, income and education. Multilevel regression analyses yielded a trend toward an interaction between 5-HTTLPR and SES predicting depression, $t(276.84) = -1.89$, $p = .060$, and an interaction between 5-HTTLPR and SES predicting anxiety, $t(227.98) = -2.17$, $p = .031$. Contrary to expectations, low SES children with the l'/l' genotype had higher anxiety relative to low SES children in the low- and moderately-expressing groups. Testing simple slopes and regions of significance in R yielded significant slopes for the l'/l' ($-.1972$, $z = 3.0832$, $p = .0021$) and s'/l' groups ($-.0901$, $z = 2.2213$, $p = .0264$), for values of the standardized SES composite near the mean (below .1089). Future analyses include using Family-Based Association Tests to maximize the power of the twin design.

Meta-analyses of 5HTTLPR, stress and depression: should we include the kitchen sink?

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The reported interaction by Caspi et al. (2003) between the length polymorphism (5HTTLPR) in the serotonin transporter gene (SLC6A4) and stressful life events on depression led to 55 follow-up studies to date (Karg et al. 2011) with inconsistent results. Three meta-analyses, likewise, have been inconsistent. Two (Munafò et al. 2009; Risch et al. 2009) found no support, while a more recent meta-analysis published this year (Karg et al. 2011) found strong support for an interaction. The current presentation considers in greater detail the studies included in this more recent meta-analysis. The biological support has only ever been for a synergistic interaction between 5HTTLPR, stress and depression, yet this meta-analysis included; (1) interactions that spread, crossed over and were even compensatory, and (2) inconsistent groupings of genotypes. This was despite Munafò et al. having previously presented a clear criticism of the heterogeneity of interactions that were viewed as replications. Further, this more recent meta-analysis included statistical interactions that were potentially artifacts of the scale of measurement. Since Item-Response Theory (IRT) methods model the underlying scale, they help control these interactions that are artifacts of scale. We present IRT methods as another avenue in helping to resolve this inconsistent literature and we consider other strategies that might be used going forward.

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Like mother, like daughter?: A quasi-experimental study of the intergenerational transmission of teenage childbearing

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Teenage childbearing is associated with poor outcomes for mothers and their children. Daughters born to teenage mothers are thought to be at increased risk for teenage childbearing themselves suggesting the intergenerational transmission of teenage childbearing perpetuates a cycle of disadvantage. Few studies have explored whether the intergenerational transmission of teenage childbearing is causal or due to unmeasured genetic and environmental confounds. It's possible that teen childbearing among daughters born to teen mothers is due to factors other than their mothers' early childbearing. The current study uses a genetically informative data from multiple Swedish national registries to test whether the association between mother's teenage childbearing and their daughter's teenage childbearing is causal. The sample included longitudinal childbearing data for 372,727 mothers (born 1957–1965) and 563,419 daughters. Information about maternal background (maternal educational achievement, income and criminal history) was included in the models, as well as father's age and birth order. Multi-level, Cox regression models were used to test the intergenerational association between and within families. Cousin and children-of-twins comparisons were used to control for unmeasured environmental factors shared by offspring of adult sisters that could otherwise differ between unrelated families. Between family-comparisons showed daughters born to teenage mothers were at increased risk of teenage childbearing (HR = 3.1, 95% CI = 2.9–3.2); including maternal covariates attenuated the association (HR = 2.6, 95% CI = 2.4–2.7). Comparisons of half cousins (HR = 7.8, 95% CI = 2.2–27.7), full cousins (HR = 2.2, 95% CI = 1.7–2.7), children born to DZ (HR = 2.2, 95% CI = 0.9–5.3) and MZ twin sisters (HR = 4.4, 95% CI = 1.6–11.5) showed the association persists after accounting for environmental and some genetic factors shared within an extended family. Results support a causal interpretation of the intergenerational transmission of teenage childbearing.

Heritability of cardiac sympathetic control at rest and during stress and the contribution of the Gln27Glu beta-2-adrenergic receptor polymorphism

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Individual differences in sympathetic nervous system activity at rest and in response to psychological stress contribute to the variance in many cardiovascular disease risk factors. In a number of different adolescent and adult twin family samples (totaling 624 complete twin pairs, 320 parents, and 193 singleton siblings) we used impedance cardiography to measure the pre-ejection period (PEP) at rest, during active and passive coping tasks, and in ambulatory recordings. The PEP is a measure of cardiac sympathetic control that reflects beta-adrenergically determined changes in cardiac contractility. Heritability of the PEP was lowest during sleep (48%) but increased in more demanding situations with peak levels during challenging mental stressors (74%). In a subset of 1187 subjects, the PEP at rest was significantly shorter in males with a CC genotype in the functional variant rs1042714 (Gln27Glu) of the beta-2-receptor (ADBR2) gene compared to male CG and GG groups. In contrast, in females the GG genotype had significantly shorter PEP than carriers of the C allele. In a mixed model ANOVA with family as a random factor, the sex-by-genotype interaction was significant ($p < 0.0001$, for MZ only one twin per pair was used). No genotype effects were found on the decrease in PEP during stress. The ADBR2 is crucial in translating increases in sympathetic activity to increases in left ventricular contractility (seen as decreases in PEP). At rest, the Gln27Glu C allele seems to cause a larger effect of sympathetic activity on contractility than the G allele in males, whereas the reverse is true in females.

Increasing GWAS sample size using item response theory: A pilot study of the personality consortium

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There is a long tradition in behavior genetics to study the genetic influences on personality traits in twin and adoption designs, demonstrating heritability for all main dimensions of personality (Bouchard et al. 1990, Science 250, 223–228; Bouchard & Loehlin, 2001, Behav Genet 31, 243–273). Recent genome-wide association (GWA) studies have suggested a handful of genetic variants that may explain the heritabilities, but effect sizes are very small and replication has proven difficult. One way to increase the chances to find the genetic variants is to combine data from multiple samples using multiple personality instruments. To this end, we extended the NEO personality consortium (De Moor et al. 2010, Mol Psychiatry In press,) with samples in which personality was assessed with the Eysenck's Personality Questionnaire (EPQ), Cloninger's Temperament and Character Inventory, the Minnesota Multiphasic Personality Inventory and others. Over 20 cohorts are now included with a total sample size of ~113,000 subjects with personality data, of which ~66,000 subjects currently have GWA data. We propose to use Item Response Theory (IRT) analysis to map the personality data from the different questionnaires to the same constructs. Here, we report first results of a study for Neuroticism conducted in two of the largest samples with personality data, the Netherlands Twin Register and the Australian Twin Register. IRT analysis shows that the Neuroticism scales from the NEO and EPQ to a large extent measure the same

construct. Moreover, the Neuroticism scale of the NEO is measurement invariant across countries.

Statistical power to detect causality in the co-twin control design

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The co-twin control design is commonly used in behavior genetics to test for causal relationships among phenotypes. For example, the MZ/DZ discordant twin design has been used to test for the causal effect of stressful life events on depression, and for the effect of cannabis use on other drug use (Kendler et al. 1999, Am J Psychiatry 156, 837–841; Lynskey et al. 2003, JAMA 289, 427–433); and the MZ/DZ intrapair differences method has been used to test for the effect of the amount of exercise on depressive symptoms (De Moor et al. 2008, Arch Gen Psychiatry 65, 897–905). Despite of the common use of the co-twin control design, little is known about the statistical power of this design to detect causal relationships. The main aim of this study was to investigate to what extent and under what conditions the co-twin control method is able to reliably detect a causal relationship. To this end, we simulated bivariate phenotypic continuous data of twins generated under a causal model (Heath et al. 1993, Behav Genet 23, 29–50). The effect of the following four factors on the power of the intrapair differences method was investigated: sample size (200, 500 and 1000 twin pairs), the MZ/DZ ratio (2:1, 1:1, 1:2), the strength of the causal relationship (standardized values of 0.1, 0.15, 0.25, 0.50) and the variance decomposition of both the causative and effect phenotype. We found that large sample sizes (1000–3000 pairs) are needed for small effect sizes (0.10–0.15). Including DZ pairs substantially increases power. Further, power increases with a larger MZ:DZ ratio and a larger proportion of variance due to unique environmental factors.

Genetic variance of body mass Index from childhood through adulthood

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Much attention is given to body mass index (BMI) and its relationship to health. However, little is known about the stability of genetic (A), common environmental(C), and unique environmental (E) factors which contribute to BMI variance from childhood into adulthood. This study evaluates the magnitude and stability of A, C, and E and correlation within A, C, and E across time.

Data on height and weight were collected and used to calculate BMI for 2,942 twins from the Swedish Twin Registry: Swedish Twin Study of Child and Adolescent Development at ages: 8–9 years (parent report; wave 1); 13–14 years (parent and twin report; wave 2); 16–17 years (parent and twin report; wave 3); 19–20 years (twin report; wave 4). Puberty stage was collected at wave 2. Parent and twin Cholesky decomposition models were fit to assess the magnitude and stability A, C, and E over time. Puberty status was entered as a definition variable moderating means at wave 2 only.

Males were in beginning-midpuberty and female were in mid-advanced puberty. Results from showed similar trends in parent and twin models. Using parent report from wave 1 and twin report from wave 4, A increased from childhood to adulthood: wave 1 = 0.42 and 0.56 and wave 4 = 0.68 and 0.69 for males and females, respectively. For males, the largest increase was between wave 1 and wave 2 in the parent model. In females, results from parent and twin models showed the largest change was between wave 2 and wave 3. C decreased between wave 1 = 0.43 and 0.33 and wave 4 = 0.08 and 0.04 in males and females, respectively. Genetic factors are largely responsible for phenotypic correlation.

Factors important in BMI variance change over growth and appear to stabilize in late adolescents and adulthood.

BMI fluctuation using an extended-twin family design

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Independent of obesity, body mass index (BMI) fluctuations are associated with adverse health outcomes. The current study sought to determine the role of genetic and environmental factors in individual differences in BMI fluctuation using the extended twin-family model (ETF).

Health and Lifestyle Questionnaires were obtained from 28,492 individuals from the Virginia 30,000 (VA30K) dataset including twins, parents, siblings, spouses, and children of twins. From self-reported height and weight, BMI fluctuation was calculated as the difference between highest (non-pregnancy) and lowest BMI after age 18, for individuals 18–80 years. The full EFT model was applied to data to estimate the significance and contribution of genetic and environmental factors, cultural transmission, and assortative mating components to BMI fluctuation. We modeled sex-specific additive and dominant genetic effects and parental, non-parental, twin, and unique environmental effects.

Means could be equated within sex and generation; the model included age moderation on means. No significant qualitative sex differences were observed as male specific genes could be dropped, and correlations between male and female shared environment, twin environment and dominance could be fixed to one. Cultural transmission was non-significant. Of the total variance in BMI fluctuation the following represent the approximate percentages attributable to each source: 14 and 41% additive genetic; 15 and 13% genetic dominance; 45 and 36% unique environmental; and 26 and 10% common environmental effects for males and females, respectively. Assortative mating increased the genetic variance by a small percentage. We acknowledge dominance is confounded with age-specific and gene-by-age effects.

A substantial amount of individual differences in BMI fluctuation appeared to be accounted for by genetic factors of which a significant portion were due to dominance factors. Shared environmental factors also contributed significantly to the variance of BMI fluctuation.

Moderation of genetic and environmental effects on externalizing by childhood maltreatment

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Childhood maltreatment experiences are associated with increased risk of drug addiction (e.g. K.S. Kendler et al., 2000, Arch Gen Psychiatry, 57, 953–959; S.E. Ullman et al., 2005, J Stud Alcohol, 66, 610–619) as well as other non-substance externalizing behaviors (C. Smith & T.P. Thornberry, 1995, Criminology, 33, 451–481). Models of externalizing support the existence of a general externalizing risk factor (i.e., a higher-order factor that explains substantial variance shared among individual externalizing-related disorders) that is substantially affected by genetic influences (e.g. K.S. Kendler et al., 2003, Arch Gen Psychiatry, 60, 929–937; R.F. Krueger et al., 2002, J Abnorm Psychol, 111, 411–424). We tested the moderating effect of childhood maltreatment exposure on the influence of genetic and environmental factors on externalizing behaviors in the Minnesota Twin Family Study. Data were available from 1198 same-sex twin pairs assessed for substance dependence (alcohol, marijuana, and cocaine) through age 25, conduct disorder prior to age 15, and adult antisocial behavior from age 15 through 25. We fit moderated univariate Cholesky models to test the effect of physical and sexual maltreatment during childhood on the relative influence of genetic and environmental factors on variance in externalizing. Compared to individuals who did not report experiencing either form of maltreatment, exposure to either physical or sexual maltreatment increased the variance in externalizing attributable to shared environmental factors.

Models of gene-environment interaction for adolescent substance use and externalizing behavior

Danielle Dick; Virginia Institute for Psychiatric Genetics

Submitted as part of symposium: Gene-Environment Interaction in Substance Use and Externalizing Behavior: Taking Genetic Research to Minority Populations and Rethinking Our Models.

A growing number of twin studies have documented environmental moderation of the importance of genetic influences on substance use and externalizing disorders. These include environments across a number of domains, including religiosity, marital relationships, parenting, peer, and neighborhood factors. A unifying theme that emerges across these examples of gene-environment interaction is one of social opportunity versus control: environments that are more controlling and structured appear to reduce opportunities to express genetic predispositions for substance use (resulting in reduced genetic variance), whereas environments that allow greater opportunity allow more room to express genetic predispositions, leading to greater genetic variance. To this end, these studies appear to converge on a mechanism for gene-environment interaction that appears to be particularly salient in substance use. Interestingly, the emerging literature on gene-environment interaction in substance use with respect to measured genes has developed almost entirely independently of the twin literature and focuses almost entirely on stress-response. This presentation will aim to integrate these literatures and move toward a more developed theory of mechanisms involved in gene-environment interaction in substance use. Further, the samples that have been studied with respect to gene environment interaction and substance use are not representative of much of the US population. For many youth, there are likely salient environmental influences (e.g., nontraditional family structures, exposure to poverty, discrimination) that are not currently captured in our models of gene-environment interaction and pathways of risk for substance use problems. Expanding our models of gene-environment interaction to incorporate a broader set of risk and protective factors, and integrating these into theoretical models, will be critical to advancing understanding of pathways of risk for substance use.

Genotype and parental sensitivity predict child externalizing problems longitudinally

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The interaction between specific genes and children's environments may be instrumental in affecting children's externalizing problem behaviors. Children with excessive repeats of the DRD4 allele who also experience negative maternal environments have been shown to exhibit increased negative behaviors. Less is known about the role of serotonin in children's behaviors. This project extended earlier work (DiLalla, Elam, and Smolen, 2009, Genetic and environmental effects on preschoolers' social behaviors. Developmental Psychobiology, 51, 451–463) to determine whether both dopamine (DRD4) and serotonin (5HTTLPR) interacted with parental sensitivity to influence externalizing behavior problems. Twins from the Southern Illinois Twins and Siblings Study (SITSS; DiLalla, 2002, Preschool social and cognitive behaviors: The Southern Illinois Twins. Twin Research, 5, 468–471) were tested at ages 3, 5, and follow-up (aged 6– 16 years). At age 3, parental sensitivity was coded during a triadic interaction with one parent and both twins. Parents rated children's externalizing problem behaviors at age 5 and again at follow-up. DRD4 and 5HTTLPR were assessed from children's buccal cells. Using multiple regression analyses, a significant effect of serotonin was found for follow-up conduct problems (beta = .71, $p = .036$), but there was no significant interaction with parental environment. However, DRD4 significantly interacted with parental sensitivity to predict externalizing problems (beta = .84, $p = .034$ for age 5; beta = .44, $p = .018$ at follow-up). Children with the higher risk genotype whose parents treated them with less sensitivity were more likely to be rated as having externalizing problems. These results support earlier work demonstrating that some children may be at genetic risk for problem behaviors if they experience more difficult, less sensitive parental environments. Children with genetic sensitivity may be adversely affected by a parenting environment as early as age 3 whose consequences extend for a number of years.

Does early sex lead to poor psychosocial outcomes? Testing causal assumptions

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Previous research suggests that early-onset intercourse may lead to negative outcomes, such as depression or substance use. However, little is known about the nature of the association between early sex and these outcomes, and few studies have accounted for unmeasured genetic or environmental influences that may confound the association between early sex and later adjustment. In the current study, we examined whether familial confounds contribute to the relationship between early sex and later depression and substance use. History of early sex (by age 16), history of cannabis use and alcohol abuse/dependence occurring by young adulthood (age 25), and current depressive symptoms were assessed in a sample of 12,126 Swedish men and women participating in the Study of Twin Adults: Genes and

Environment. The nature of the association between early sex and each putative outcome was explored by comparing outcomes among twins who differed in their experience of early sex and by estimating bivariate twin models. Early sex was reported by 24% of the sample. Individuals who engaged in early sex were significantly more likely to have used cannabis or have had problems with alcohol by age 25 or to endorse elevated levels of current depressive symptoms, but associations were no longer significant when comparing differentially exposed twins. Bivariate twin models indicated that familial factors significantly contributed to the covariation between early sex and each outcome. These analyses suggest that early sex may not lead to depression or substance abuse; instead, these associations are due to common influences shared by twins, suggesting that delaying sexual intercourse may not reduce risk for these outcomes.

Three psychopathic trait dimensions are differentially associated with reactive and proactive aggression in youth

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Despite growing research in psychopathic traits among children and adolescents in recent years, the factor structure of commonly used measures of psychopathic traits in youth samples is still unresolved and inconsistent across different measures and samples. The present study aims to study the external validity of the three-factor model of psychopathic tendencies in youth by examining differential relations between each of the three psychopathy dimensions (i.e., Narcissism, Callous-Unemotional traits, Impulsivity) and reactive and proactive aggression, which are considered important correlates of psychopathy. Relations between parent-reported psychopathic tendencies as measured by the Antisocial Process Screening Device and aggressive behaviors as measured by Dodge & Coie's reactive-proactive scale were analyzed in both clinic-referred ($n = 350$; mean age = 10.7 years) and community samples ($n = 1735$; mean age = 10.6 years), both separately and jointly. We used Structural Equation Modeling (SEM) given its allowance of substantial correlations between dimensions of aggression as well as dimensions of psychopathy. Pooled analyses that constrained equatable parameters of the SEM model across samples suggested statistically significant differences in the associations of the three psychopathy factors with reactive and proactive aggression. Specifically, after controlling for appropriate sex and age covariates, Narcissism was significantly and similarly (is this correct?) associated with both reactive and proactive aggression, whereas CU was uniquely related with proactive aggression and Impulsivity with reactive aggression. The present findings provide robust empirical support for the external validity of the three-factor model of psychopathic traits in children.

Behavior genetic analyses of psychopathic trait dimensions in children

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Psychopathy is defined as a condition characterized by affective and interpersonal features (e.g., egocentricity, lack of empathy) as well as behavioral maladaptations (e.g., impulsivity, antisocial behaviors). It is generally thought to have a strong genetic/neurobiological basis and its roots in childhood. Several behavior genetic studies of psychopathy in adults and adolescents have suggested moderate heritability for each psychopathy dimension (i.e., Grandiose/Manipulative, Callous/Unemotional, Impulsivity/Irresponsible) and moderate genetic correlations among these dimensions. The genetic and environmental influences on the development of psychopathy early in life are not well understood, however. Similar to the factor structure of psychopathy in adults, confirmatory factor analyses of the Antisocial Process Screening Device, a commonly used measure of psychopathic tendencies in children, yielded three correlated but distinct dimensions: Narcissism, Callous-Unemotional (CU) traits, and Impulsivity. Preliminary studies in pre-adolescent children suggest that CU traits are heritable and that the presence of CU traits substantially increases the heritability of conduct problems. Nonetheless, genetic and environmental influences on the other two psychopathic dimensions (i.e., Narcissism and Impulsivity) among children have not been explored. Further, in children it is not clear how much of the genetic and environmental variance is unique to each of the three dimensions of psychopathy or shared in common among them. In this study we address these questions via univariate and multivariate behavior genetic analyses in a sample of 842 twin pairs (388 MZ and 454 DZ) with an average age of 11.8 years. Univariate analyses suggest moderate genetic and non-shared environmental influences for all three dimensions. Multivariate behavior genetic analyses will be performed to explore the common and unique genetic and environmental influences underlying the three psychopathy dimensions.

Familial confounding of the association between maternal smoking during pregnancy and offspring substance use and abuse

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Most research on maternal smoking during pregnancy (SDP) comparing unrelated individuals has found a robust statistical associations with numerous measures of substance use and abuse, consistent with a strong causal inference. Recent quasi-experimental studies, however, have suggested that family background characteristics account for the statistical association between SDP and related problems, such as cognitive and behavior problems. The current study sought to explore whether background familial factors confound the relation between maternal SDP and multiple indices of offspring substance use and abuse. The analyses were based on a subset of participants from the offspring of the National Longitudinal Survey of Youth 1979, a diverse and representative longitudinal sample of male and female youth ($n = 7{,}431$ adolescents), which was weighted to yield population-based estimates.

Consistent with previous studies, maternal SDP was associated with increased risk for alcohol use during adolescence, early alcohol initiation (before 14 years old), lifetime report of alcohol impairment, lifetime cigarette use, early cigarette initiation (before 14 years old), lifetime marijuana use, early marijuana initiation (before 14 years old), and criminal convictions for substance use. The associations were robust to the inclusion of statistical covariates. But, when we compared differentially exposed siblings the magnitude of the associations between SDP and each measure of substance use and abuse

were greatly attenuated and not statistically significant. The results strongly suggest that genetic and/or environmental factors that influence all siblings in a family account for the statistical relations between SDP and offspring substance use and abuse, rather than causal influences of SDP on the developing fetus.

Association of DRD4 7R and DRD2 Taq1A polymorphisms with binge eating in patients with seasonal affective disorder

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The present study aims to investigate the relationship between polymorphisms in the dopaminergic system, binge-eating and weight gain in patients with seasonal affective disorder (SAD). This is motivated by evidence suggesting that these hallmark features of SAD may be mediated by dopamine variation (Levitan et al., 2004). Researchers have proposed the Reward Deficiency hypothesis to explain dopamine function as it relates to addictive behaviors, including overeating. According to this model, individuals with hypoactive dopaminergic systems engage in rewarding behaviors to compensate for this deficit. To extend the work of Levitan (2004), the Taq1A restriction fragment length polymorphism linked to the dopamine-2 receptor gene, in addition to the 7-repeat allele of the dopamine-4 receptor gene (DRD4), was assayed. This polymorphism is associated with blunted dopamine response, higher body mass index (BMI), and binge-eating in multiple conditions, including bulimia (Kaplan et al., 2008), and obesity (Stice et al., 2008). Seventy-five participants completed the SIGH-SAD, a semi-structured version of the Hamilton Depression Rating Scale modified for SAD that identifies atypical symptoms. Additionally, participants completed the Questionnaire on Eating and Weight Patterns (Spitzer et al., 1993), a self-administered survey assessing binge-eating symptomology defined by the DSM-IV (APA, 1994). As predicted, individuals with SAD reported higher maximal lifetime BMI, and were more likely to binge eat relative to controls. Further, there was an elevated frequency of the 7R allele in individuals with SAD, and this allele was significantly associated with self-reported seasonal variation in binge-eating and weight gain. The Taq1A A1 allele was not associated with binge-eating behavior, and was not correlated with SAD diagnosis. Given the strength of the relationship between SAD and binge-eating detected in this sample, it is surprising that neither high-risk dopamine allele was associated with eating pathology. This is likely due to the under-representation of such individuals in this sample.

Depression as a moderator of genetic risk for overweight and obesity

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The objective of this study was to determine whether a history of DSM-IV major depression (MD) moderated the risk for overweight and obesity associated with genetic risk score (GRS), which is a sum of risk alleles for body mass index (BMI) identified from a recent meta-analysis (Speliotes et al., 2010). Data came from 5986 participants in three ongoing studies: (1) the Nicotine Addiction Genetics (NAG) and two interrelated Interactive Research Program Grant (IRPG) alcohol studies (2) the Big-Sibships Study; and (3) the Extreme Discordant and Concordant Study. We used multinomial logistic regression to analyze the data, using BMI category (obese, overweight, and normal weight [referent]) as the dependent variable. The GRS was significantly associated with obesity (RRR = 1.19; 95% CI: 1.13–1.26) and overweight (RRR = 1.05, 95% CI: 1.01–1.10), and major depression was associated with obesity (RRR = 1.26, 95% CI: 1.07–1.48). There was a significant interaction between MD and the GRS for obesity, such that the GRS was only associated with obesity in those without a history of MDD (RRR = 1.24, 95% CI = 1.16–1.33). It is possible that the association between depression and weight gain outweighs the specific genetic liability to obesity. Future research will endeavor to disentangle these relationships by further exploring the complex relationship between obesity and depression.

An exploratory twin study of internalizing disorders and alcohol use problems

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Epidemiological studies demonstrate considerable overlap between internalizing disorders and alcohol problems. Twin studies have indicated that some of this overlap may be due to a shared genetic liability, and molecular genetic studies have identified genes that influence both alcohol problems and internalizing disorders. However, this literature is very limited relative to the extant genetic epidemiological literature on alcohol comorbidity that focuses on the association between externalizing disorders and alcohol problems. The current study dissects the relationship among multiple internalizing disorders—depression, social phobia, panic disorder, and agoraphobia—and alcohol use problems in a population-based sample of young adult Finnish twins. Using exploratory twin modeling, we investigate the extent to which genetic and environmental factors underlie the phenotypic associations among disorders. Furthermore, we explore whether these sources of shared liability differ across disorders or whether, for example, a single common genetic factor accounts for the genetic correlation between alcohol use problems and all measured internalizing disorders. Our findings can ultimately be used to derive genetic factor scores for use in gene-finding studies, with the goal of identifying genetic variants underlying the risk for development of the well-established, but poorly understood, internalizing subtype of alcohol use problems.

Are different kinds of parenting more effective for different children?: Considering genetic influences using an adoption design

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Parenting that is supportive, structured, and guiding can aid in the development of child regulation and help prevent emotional and behavioral problems early in life. Recently, Leve et al. (2009) found an interaction between birth mother psychopathology (conferring genetic risk) and adoptive mothers' structured parenting, where structured parenting predicted less problem behavior in adoptees at high genetic risk but more problem behavior in adoptees at low risk. Thus, specific parenting strategies may vary in their effect as a function of a child's inherited characteristics. However, it is unknown whether there are longitudinal impacts of this gene-environment interaction and whether effects are specific to structured parenting.

The present study examined longitudinal influences of structured parenting and positive reinforcement on child problem behavior. Families from the Early Growth and Development adoption study were assessed at 18, 27, and 54 months of age. The sample was split into high and low genetic risk based on birth mother psychopathology and drug use, an identical measure to Leve et al. (2009). Parenting strategies were assessed at 18 months via a microsocially coded parent–child clean-up task. Using growth curve modeling, results showed that structured parenting predicted the intercept (−.35***) of CBCL total problem behavior in the high risk group but not the low risk group, indicating moderation of child problem behavior based on genetic risk. Children at greater genetic risk benefitted from structured parenting whereas those at lower genetic risk did not. No such interaction was found for positive reinforcement (main effect only). These results highlight the utility of structured parenting strategies in the prevention of problem behavior in children at heightened risk.

Reference

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Disentangling the relationships between maternal smoking during pregnancy and co-occurring risk factors

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A robust relationship has been established between maternal smoking during pregnancy (SDP) and adverse psychological outcomes in offspring, but co-occurring familial risk factors have attenuated these associations. The current study disentangled the relationship between maternal SDP and co-occurring risk factors (maternal antisocial behavior, substance abuse, teen pregnancy, low educational attainment, and cohabitation at childbirth) in a population-based sample of full- ($n = 226{,}538$) and half-sister pairs ($n = 30{,}048$) from Sweden. Consistent with previous studies, mothers engaging in SDP (10+ cigarettes per day) were more often convicted of violent (OR = 7.57) and drug-related crimes (OR = 14.12), and were also more likely to be hospitalized with alcohol (OR = 8.25) and other drug problems (OR = 9.74). In addition, maternal SDP was associated with a greater probability of other offspring risk factors, including teen pregnancy (OR = 2.73), being born into a single-parent household (OR = 3.92), and low maternal educational attainment (OR = 4.46). Of the variance associated with SDP, 45% was attributed to additive genetics and 53% was attributed to unshared environment. In bivariate analyses, genetic factors accounted for 18% (non-drug- or -violent crimes) to 37% (drug-related crimes) of the covariance between SDP and co-occurring risk factors, with unshared environmental factors accounting for the remaining covariance. The results suggest that the intergenerational transmission of genes conferring risk for antisocial behavior, substance abuse, and an adverse rearing environment for offspring may, at least partially, influence the associations between maternal SDP and offspring adverse outcomes.

The relationship between executive function and antisocial behavior from age 9–16: A longitudinal twin study

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Behavioral disinhibition and executive dysfunction (EDF) are two key aspects of self-regulation that serve as risk factors for the development of antisocial behavior (ASB). In spite of the well established correlation between EDF and ASB, we do not yet know (1) the direction of the relationship itself, i.e., whether ASB may be result or cause of EF deficits during development, and (2) the extent to which the relationship is mediated by genetic and environmental factors. Cross-lagged regression models were used to investigate these questions in a longitudinal twin study based on data from two occasions when the twins were age 9–10 (Time 1) and age 14–16 (Time 2). Preliminary phenotypic results demonstrated a strong association between EF and ASB at Time 1 ($r = .27$, $p < .01$), Time 2 ($r = .29$, $p < .01$), and longitudinally ($r = .25$, $p < .01$). In addition, ASB at Time 1 also correlated with future EF at Time 2 ($r = .24$, $p < .01$), which is, at the very least, suggestive of bi-directional effects. A fully cross-lagged model was found to best fit the data, such that deficits in early EF led to higher rates of later ASB (b12 = 0.12, Est./S.E. = 2.318), and early ASB affected later EF (b21 = 0.10, Est./S.E. = 2.58) while controlling for their pre-existing relationships and stabilities over time. Genetic factors contributed to the variation in EF from ages 9–16 (Time 1: 26%; Time 2: 29%), with no effect of shared environment. For ASB, genetic factors accounted for 43% of the variance during Time 1 and 55% of the variance during Time 2, with the remaining variance being comprised of shared environmental (Time 1: 20%; Time 2: 16%) and non-shared environmental factors (Time 1: 37%; Time 2: 29%). Biometric cross-lagged analyses will be used to examine the genetic and environmental contributions to the direction of effects between EF and ASB; these analyses are currently underway.

Reliability of factor scores and related methods with missing data & the impact of genetically-informative designs

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Researchers have long been interested in the estimation of individually varying latent traits, but methods for estimating factor scores and related parameters have seen considerable debate. A number of algebraic or

regression-based methods exist for the estimation of factor scores (see Lawley & Maxwell, 1971 for review). While several studies have investigated the reliability for several estimation methods for exploratory models, the reliability of factor scores has yet to be investigated for confirmatory factor models, especially in the context of missing data.

A series of simulation studies are presented to compare the reliability of maximum likelihood factor score estimation to regression methods and sum scores. Results show maximum likelihood factor score estimation for continuous data to be superior to both regression methods and sum scores, showing greater benefits in the presence of missing data. A second simulation found similar results for binary data, with a 2PL item response model performing equally with the maximum likelihood method. Reliability for continuous data were found to follow Guttman's (1955) equation for communality, whereas reliability for binary data require an added correction for attenuation be added to this equation.

Further simulations were used to investigate the impact of clustered data in a genetically-informative design. Given identical models and sample distributions, factor scores estimated for 250 twin pairs were found to be more reliable than factor scores estimated for 500 singletons, with stronger gains in reliability found when heritability increases. Implications and estimation in OpenMx will be discussed.

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Exploring the role of retrospective perceptions of parental care in understanding associations between marital satisfaction and parent–child closeness

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Previous research indicates that adults' marital satisfaction and their relationship with their own children are associated. Attachment theory proposes that similarities between these two family subsystems are influenced by the quality of one's relationships with attachment figures during childhood. The current study tests this hypothesis and examines the degree to which early childhood experiences (assessed through retrospective reports of parental warmth and control) accounts for covariance between adults' marital satisfaction and relationship with their own children. In keeping with attachment theory, it was hypothesized that childhood experiences would account for environmental contributions to covariance between adults' current marital satisfaction and relationship quality with their own children.

Participants for the current study were drawn from The Twin/Offspring Study in Sweden (TOSS), a sample consisting of 909 male and female same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs as well as their spouses and children. The Parental Bonding Instrument (PBI) was used to assess retrospective reports of maternal and paternal warmth and control during childhood. The twins' current marital quality and relationship with their own children were assessed via the Dyadic Adjustment Scale (DAS) and a parent–child closeness measure. Retrospective perceptions of parental care explained 13–25% of the covariance between reported marital satisfaction and parent-reports of parent–child closeness, and 55% of the covariance when children reported on their closeness with their parents. In all models, retrospective perceptions of parenting accounted for a significant portion of environmental contributions to covariance between marital satisfaction and parent–child closeness. However, genetic factors explained a significant portion of the remaining covariance between marital satisfaction and parent–child closeness. Results indicate that early experiences with parents recalled retrospectively in adulthood as well as genetically influenced characteristics interact in shaping the emotional climate of the family.

A national resource for genetic research in behavioral & social science: The health and retirement study

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Since 1992, the Health and Retirement Study (HRS, a cooperative agreement between the National Institute on Aging (NIA) and the University of Michigan) has been the largest, most representative longitudinal study of Americans 50 years and older. Built on a national probability sample with oversamples of minorities, it is the model for a network of harmonized international longitudinal studies that monitors work, health, social, psychological, family and economic status, and assesses critical life transitions and trajectories related to retirement, economic security, health and function, social and behavioral function and support systems. The HRS also features linkages to Medicare claims, National Death Index, and administrative earnings and benefits data from Social Security. The data are available to the public, with some restrictions on access to administrative records.

Using funds from the American Reinvestment and Recovery Act (ARRA),the HRS is now genotyping 2.5 million single nucleotide polymorphisms (SNPs) on respondents using Illumina's Human Omni2.5-Quad (Omni2.5) BeadChip methodology. Genotype data on about 13,000 respondents will be deposited in dbGaP by the end of 2011. Data from an additional 7,000 respondents will be added over the next 2 years including an expansion of the minority sample to over 3,300 African-American and 2,600 Hispanic-Americans. The rich longitudinal measurement across domains of health, psychological characteristics, social networks, and economic status and behavior in the HRS creates an unparalleled body of phenotypic data that can now be paired with genotypic characterization of 2.5 million SNPs. Valuable as a replication sample for many established GWA studies, this resource, building on a study already widely known in behavioral aging research, will be one of the first large-scale studies to combine genetics with behavioral phenotypes, creating a platform for discovery.

Does the post-adoption environment significantly improve the verbal performance of young Russian adoptees

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Children adopted from Eastern Europe are known to have an elevated risk for displaying problems in multiple developmental areas. Two questions that are of continuing interest in foreign adoption studies are the extent to which a facilitative post-adoption environment may enhance selected abilities in this at-risk group and for whom such an environment may exert the most positive effect. Because of its unique design, the present study provides preliminary evidence of post-adoption environmental influences in a group of 72 children between 2 and 9 years of age who were adopted into the United States from Russia. The performance of the adoptees is directly compared to the performance of three age and gender-equalized groups: 55 non-adopted children in the US (US controls); 61 non-adopted children raised in Russia (RUS controls); and, importantly, 61 children who remained in Russian orphanages over the study period (orphans). One "fluid" measure (nonverbal problem solving) and one "crystallized" measure (a standardized language test) were selected for study. Significant group differences were found for both of these measures ($p < .0001$). Post-hoc analyses revealed that children adopted into US homes performed comparably to institutionalized orphans in non-verbal problem solving. The orphans performed significantly more poorly than the adoptees (and the controls) on the standardized test of language, which relies upon learned information and cultural exposure to linguistic concepts. When compared with US controls, the adoptees performed significantly more poorly on both measures, although most scores were in the average to low-average range. The only predictors that were associated with language performance in the adoptee group were age at adoption ($r = -.506$) and length of time in the home ($r = .307$). None of the Family Environment Scale subscales were associated with language achievement among the adoptees.

Candidate genes for aggression and antisocial behavior: A meta-analysis of the 5-HTTLPR and MAOA-uVNTR

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Antisocial behavior—behavioral tendencies that reflect disregard for social norms and the rights of others—is exhibited in elevated levels in clinical populations and associated with negative outcomes, such as violent crime, alcoholism, and drug use. Genetic influences have been estimated to explain approximately 50% of the variance in antisocial phenotypes. Variation within the serotonergic system has been associated with aggression in animals and humans, leading to hypotheses that individual differences within serotonergic system genes may underlie antisocial phenotypes. Nonetheless, candidate gene studies examining the main effects of common variation within serotonergic system genes have yielded small, inconsistent findings thus far. We conducted a meta-analysis of associations between antisocial behavior and the two most commonly examined serotonergic system variants: the serotonin transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene and a 30 bp VNTR within the promoter of the monoamine oxidase A gene (MAOA-uVNTR). Specifically, we examined: (1) whether the putative "risk" alleles of each marker had significant main effects on antisocial phenotypes across studies, (2) whether there was significant heterogeneity in study effect sizes, and (3) whether demographic or methodological differences contributed to the observed heterogeneity across studies. We found small but significant main effects for the 5-HTTLPR (OR = 1.389, $p < 0.001$, 95% CI [1.179–1.637]), but not the MAOA-uVNTR (OR = 1.063, $p = 0.433$, 95% CI [0.913–1.237]). In addition, there was significant heterogeneity in effect sizes for both markers. Regression analyses suggested that this heterogeneity could be partially explained by sample age, sex and ethnic composition. Overall, it appears that the most commonly examined serotonergic variants contribute only a small portion of the variance in antisocial phenotypes, and it is thus important that future studies focus on additional common and rare variants within these and other genes known to affect serotonergic function.

Odor identification and ApoE impact normative cognitive aging

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Research indicates that apoliprotein E (ApoE) plays a role in the development of Alzheimer's disease (AD) and possibly in the cognitive decline associated with normative aging. More recently, researchers have shown that ApoE is expressed in olfactory brain structures, and a relationship among ApoE, AD, and olfactory function has been proposed. In the current analyses, we investigated the contribution of ApoE and odor identification in decline trajectories associated with normative cognitive aging in various domains, using longitudinal data on cognitive performance available from the Swedish Adoption/Twin Study of Aging. Data on both ApoE status and olfactory functioning were available from 455 individuals ranging in age from 50 to 88 years at the first measurement occasion. Odor identification was measured via a mailed survey. Cognitive performance was assessed in up to 5 waves of in-person testing covering a period of 26 years. Latent growth curve analyses incorporating odor identification and ApoE status indicated a main effect of odor identification on the performance level in three cognitive domains: verbal, memory, and speed. Twins with more errors in odor identification had lower mean levels of performance on the cognitive factors than those with few odor errors. A main effect of ApoE on rates of decline was indicated for all four factors, but did not achieve statistical significance for the memory factor. Cognitive performance of individuals with at least one e4 allele declined faster after age 65 than individuals with no e4 alleles. Only 11 individuals in the sample carried two e4 alleles; however, results indicated a possible olfaction x ApoE interaction effect on level of performance and a differential impact on rates of decline for this subset.

Hair pulling disorder (Trichotillomania): Genes, neurobiology, and a model for understanding impulsivity and compulsivity

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Hair pulling disorder (trichotillomania) affects at least 3.7 million people in the United States and results in marked functional impairment in those afflicted with the disorder. The aim of this article is to review and synthesize recent efforts to characterize distinct pulling styles, referred to as automatic and focused pulling, among patients who pull their hair. These pulling styles exhibit facets to basic behavioral processes, impulsivity and compulsivity, characteristic of

several classes of disorders (e.g., obsessive–compulsive spectrum disorders, impulse control disorders). Recent findings from the animal literature and human studies examining the neurobiology of hair pulling suggest that several candidate genes (e.g., SAPAP3, Hoxb8) and biological pathways (e.g., dopamine, serotonin) may be relevant to developing a better understanding of these processes and, in turn, the pathogenesis of hair pulling. Because nearly all patients, children (10+ years of age) and adults, who pull their hair exhibit both automatic and focused pulling, hair pulling may also provide a model for advancing science's understanding of the pathogenesis and treatment of related disorders (e.g., Tourette's disorder, obsessive–compulsive disorder, body dysmorphic disorder, pathological gambling). Alternative conceptualizations of hair pulling and future areas of research are discussed.

A within-family comparison of paternal age in siblings discordant for schizophrenia

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Background: Advancing paternal age has been linked to schizophrenia. Although never directly tested, this association is hypothesized to be a result of de novo mutations accumulating during a man's life span and thus increasing with advancing paternal age. Alternative hypotheses suggest that the association is explained by characteristics of older fathers. To assess this we used within-family controls and compared paternal age at birth of siblings discordant for schizophrenia.
Method: Individuals with schizophrenia and discordant siblings were identified with Swedish nation-wide registers. Affected individuals were defined as having one or more ICD schizophrenia diagnosis in the Hospital Discharge Register. A total number of 9,942 siblings affected with schizophrenia and 17,921 healthy siblings were included in the main analyses. Healthy controls ($N = 99{,}420$) with healthy siblings ($N = 182{,}374$) were analyzed to contrast the result of the within-family design.
Results: Fathers of affected siblings were on average 0.44 years older as compared to the mean paternal age within the family. This difference was statistically significant ($p < 0.0001$). The paternal age difference between affected and unaffected siblings could not be explained by truncation bias since the results where statistically significantly different compared to frequency matched controls. The results of sub-analyses conducted on families with only two siblings were consistent with the main results.
Discussion: We have, for the first time, tested the paternal age effect on schizophrenia by using within-family controls. We found an association between paternal age and schizophrenia when comparing siblings discordant for schizophrenia. Our study shows that the paternal age effect is present even when paternal, maternal or family characteristics are fixed and the results support the notion of a causal mechanism.

What makes you happy? Exploring the genetic and environmental dimensionality of well- and Ill-being

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Americans are living longer. Therefore, an important public health goal is to find ways to maximize health and happiness throughout the adult lifespan. Subjective well-being (SWB) is associated with better health and longevity; however, the current state of the measurement of well-being leaves many questions unanswered. Are happiness and satisfaction synonymous with well-being? Is well-being simply at the other end of a continuum from "ill-being" (e.g., neuroticism, depression)? Is well-being uni-dimensional or multi-dimensional? How do measures of well-being map onto genetic or environmental sources of variation? The optimal way these types of well-being constructs should be "lumped" or "split" remains unresolved. To address these questions, we examined multiple measures of SWB collected from 1237 male twins ages 51-60 who participated in the Vietnam Era Twin Study of Aging (VETSA). Measures included the Ryff Psychological Well-Being Scale (PWB), trait well-being from Tellegen's Multidimensional Personality Questionnaire (MPQ-WB), the Center for Epidemiologic Studies Depression Scale (CESD), the Rosenberg Self-Esteem (RES), and current Life Satisfaction (1-item). Heritability estimates of the measures ranged from .21 (Life Satisfaction) to .51 (PWB). Phenotypic factor analyses indicate 1 factor underlying the 5 scales; however, multivariate twin analyses find 2 genetic factors and 1 unique environmental factor. PWB, CESD, and RSE load most strongly on the first genetic factor, whereas MPQ-WB and Life Satisfaction load most strongly on the second genetic factor. These commonly used measures of well- and ill-being have substantial overlap at the phenotypic level; however, at the genetic level measures involving self-evaluation and comparison with others (first genetic factor) appear to involve different genes than those involving affective components of SWB (second genetic factor). Better differentiation of genetic influences in such measures will likely facilitate the discovery of genes that predispose some people to remain happy and mentally healthy even in the face of adversity.

Heritability, assortative mating and gender differences in violent crime: Results from a total population sample using twin, adoption, and sibling models

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Research addressing genetic and environmental determinants of antisocial behavior show substantial variability across studies. Likewise, evidence for etiologic gender differences is mixed, and estimates might be biased due to assortative mating.

We used longitudinal Swedish total population registers to estimate the heritability of objectively measured violent offending (convictions) in classic twin ($N = 36{,}877$ pairs), adoptee-parent ($N = 5{,}068$ pairs), adoptee-sibling ($N = 10{,}610$ pairs), and sibling designs ($N = 1{,}521{,}066$ pairs). Type and degree of assortative mating were estimated from comparisons between spouses of siblings and half-siblings, and across consecutive spouses.

Heritability estimates for the liability of violent offending agreed with previously reported heritability for self-reported antisocial behavior. While the sibling model yielded estimates similar to the twin model (A = 55%, C = 13%), adoptee-models appeared to underestimate familial effects (A = 20–30%, C = 0%). Assortative mating was moderate to strong ($r_{spouse} = 0.4$), appeared to result from both phenotypic assortment and social homogamy, but had only minor effect on variance components. Finally, we found significant gender differences in the etiology of violent crime.

Longitudinal analyses of inhibitory control and ADHD-related behavior problems and symptoms: Toddlerhood, first grade and early adolescence

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Inhibitory control (IC) is a dimension of child temperament involving the ability to appropriately regulate behavior. In middle childhood, low levels of IC are associated with higher levels of non-clinical behavior problems and ADHD. Multiple twin studies indicate that IC is genetically influenced (J. R. Gagne & K. S. Saudino, 2010; J. R. Gagne & H. H. Goldsmith, 2011). In addition, researchers have examined genetic and environmental covariance between IC and behavior problems in toddlerhood (J. R. Gagne & K. S. Saudino, invited revision) and school age (K. Lemery-Chalfant, L. Doelger, H. H. Goldsmith, 2008). This longitudinal twin investigation focuses on IC, ADHD-related behavior problems, and ADHD symptoms across toddlerhood, first grade and early adolescence.

Participants included 358 MZ and 694 DZ twin pairs from the Wisconsin Twin Project. Mother ratings of IC were collected in todderhood and first grade, and mother ratings of ADHD-related behavior problems and ADHD symptoms were collected in first grade and early adolescence. Phenotypic correlations between IC and ADHD measures ranged from −.27 to −.66, indicating that children with lower IC had higher maladjustment. MZ correlations exceeded DZ correlations, suggesting the presence of genetic influences. Univariate analyses indicated that genetic influences were significant for all variables (heritabilities ranged from .63–.73). Multivariate Cholesky decomposition models yielded parameter estimates consistent with the univariate models, and significant genetic correlations between IC and ADHD measures (−.44 to −.97). Results show that toddler IC is associated with ADHD-related measures in first grade, and first grade IC is related to ADHD measures concurrently and in early adolescence. These findings also indicate that earlier assessments of IC can be considered genetic risk factors for later ADHD-related behavior problems and symptoms. Future analyses will include behavioral assessments of IC in first grade and associations with candidate genes.

Associations between child anger and parenting during toddlerhood: Underlying mechanisms

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Toddlers' anger proneness (AP) describes their predisposition to experience and express anger, and is predictive of child behavior problems. Current research suggests that parents play a key role in translating AP into behavior problems. For example, children's AP may evoke more parent negativity, and create an environment conducive to behavior problems (child effects model). Alternatively, parents' may regulate the expression of children's AP (parent moderation of risk model), and affect the potency of AP as a risk factor. This study examined both mechanisms within the Boston University Twin Project (BUTP).

BUTP includes 144 Monozyogotic (MZ) and 168 Dizygotic (DZ) same-sex toddler twin pairs (Mage = 2.07 years). Mothers completed a series of questionnaires that rated children's AP and their own parenting negativity. Maternal negativity and toddler AP were significantly correlated (r = .29). A Cholesky model was used to estimate genetic and environmental contributions to toddlers' AP and maternal negativity, and to their covariance. Consistent with the child effects model, genetic factors associated with AP explained nearly all (93%) of the covariance between AP and maternal negativity, and a significant portion of the total genetic contributions (37%) to maternal negativity. The remaining variance in AP and maternal negativity was explained by unique genetic, shared and nonshared environmental factors. A moderation model (Purcell, 2002, Twin Res, 5, 554–571) was used to examine whether maternal negativity moderates genetic and environmental contributions to AP. Within the context of high maternal negativity, genetic factors accounted for most variance in AP. However, within the context of low maternal negativity, shared environmental factors accounted for most variance in AP. These findings indicate that while children's AP can affect parenting (child effects model), parents' negativity also modulates the expression of AP, potentially enhancing or diminishing children's genetic-based vulnerability for future emotional and behavioral problems (parent moderation of risk model).

Is it all in the genes? Family environment predicts externalizing in preschool twins

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Understanding complex psychological phenomena requires knowledge of how genes and the environment influence behavior. This study explored how genes, a chaotic home environment, and family conflict contribute to externalizing behavior in a sample of 5-year-old twins. Externalizing behaviors in children have demonstrated moderate heritability. Similarly, environmental factors such as a chaotic home environment have been shown to influence these behaviors. However, no studies have examined whether these environmental factors predict externalizing behavior above and beyond genetic influence in a sample of preschool-aged children. This is an especially important age group to examine, as they are about to enter into school environments where externalizing behaviors disrupt learning and forming peer relationships. The sample consisted of 175 5-year-old twin pairs from the Southern Illinois Twins and Siblings Study (DiLalla, L.F., 2002, Preschool social and cognitive behaviors: The Southern Illinois Twins. Twin Research, 5, 468–471). Utilizing a DeFries-Fulker regression model, we explored whether environmental factors (family chaos and family conflict) were able to account for variance in externalizing behaviors after controlling for genetic influence. Parent-report measures of chaos in the home, conflict in the home, and children's externalizing problems were collected for each twin. Results demonstrated that, once genetic influences were controlled, family chaos and family conflict were still significantly related to externalizing behavior. These findings suggest that the relation between family environment and externalizing behaviors in

twins does not reflect shared genes, but rather that the family environment contributes an independent influence on externalizing problem behaviors.

An eye-tracking study of attentional biases in children of depressed mothers: Applying an aggregate genetic risk score approach to studying G x E interactions

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We previously reported that children of mothers with a lifetime history of MDD exhibited an attentional bias specifically for sad faces, with evidence that this link was stronger among carriers of the 5-HTTLPR short allele than among children homozygous for the long allele (Gibb et al., 2009). Contrary to other research (Kujawa et al., 2011), however, we found that children of depressed mothers exhibited attentional avoidance of sad faces rather than preferential attention.

In this study, we extend our previous findings in two ways. First, rather than focusing only on variation in a single gene (5-HTTLPR), we took an aggregate genetic risk score (AGRS) approach and focused on cumulative level of risk across several genes within the serotonergic system that code for serotonin transporters (5-HTTLPR), receptors (HTR2A), and synthesis/breakdown (TPH2). Second, we sought to provide a more fine-grained assessment of attentional allocation by utilizing eye-tracking rather than relying on reaction times within the context of the dot probe task.

Participants were children aged 8–14 and their mothers participating in a larger study of the intergenerational transmission of depression. Mothers were required to have either (i) a history of MDD during their children's lifetime, or (ii) no lifetime history of any mood disorder. Although we did not find significant effects for overall duration of gaze to each emotion type, we did find a significant Mother MDD $\times$ AGRS $\times$ Emotion interaction predicting children's average duration of fixations. Specifically, extending our previous findings, we found children of depressed mothers with higher compared to lower AGRS scores exhibited shorter fixations to sad faces. This effect was specific to sad faces and was not observed for happy or angry faces. Finally, supporting the utility of an AGRS approach, none of the genes used to compose the AGRS had significant effects when considered individually.

Effects of ancestry on asthma

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Background: How are individual differences in ancestry expressed in twin data? Our aim was to characterize the contribution of racial admixture to individual differences in twin pair similarity for asthma in a sample of Puerto Rican children. It is hypothesized that between family differences in ancestry contribute to (i) genetic similarity because of the genetic consequences of assortative mating or (ii) because of passive G-E correlation, expressed as shared (C) environmental effects.
Methods: Data were based on a sample of 334 monozygotic and dizygotic twin pairs with complete phenotypic and genotypic data. Asthma was assessed with seven maternally rated items measuring frequency of hospitalization and use of medications, as well as frequency and severity of symptoms such as coughing and wheezing. Paternal and maternal ancestry were based on a panel of 46 autosomal ancestry informative markers used to estimate group and individual ancestry proportions obtained using a Bayesian approach. Group contributions in this Puerto Rican sample were estimated at 53% European, 41% African, and 6% Amerindian.
Results: We fitted univariate analyses in Mx to asthma symptoms and compared models with and without population admixture included as a threshold effect. Our results show that between family differences in ancestry account for small changes in C for asthma.
Conclusion: Small proportions of individual differences in asthma symptomatology appear to be attributable to passive G-E correlation. This suggests that genes for ancestry may in part correlate with individual differences in environmental risks of asthma.

Genetic analysis of behavioral/emotional problems in 7-12 years old Russian-speaking children (teachers reports)

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Background: Previous genetic studies of child behavioral/emotional problems were conducted in developed countries. Objective: To investigate the relative contributions of genetic and environmental factors to individual differences in behavioral/emotional problems in Russian-speaking children. Methods: Teachers Report Form (TRF, Achenbach, T. M. Manual for the Teacher's Report Form and 1991 Profile, Burlington: Vermont, 1991) was administered to teachers of 606 7–12 years old twins ($M = 9.43$; $SD = 1.707$) recruited in Tver and Izhevsk (Russia) and Bishkek (Kyrgyzstan). Model-fitting was used to assess the contributions of genetic and environmental factors. Results: The best fitting model for the majority of scales was ACE model that included additive genetic, shared environment and non-shared environment components. Heritability estimates varied from 0.19 to 0.79. Conclusions: Our findings concur with those from developed countries. There are important environmental, as well as genetic factors which contribute to phenotypic variance of teachers' reports of behavioral/emotional problems in 7–12 years old Russian-speaking children.

Genetic and environmental influences on individual differences in "Big Five" personality traits in adolescent and young adult Russian twins

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Heritability of personality traits is a well-documented phenomenon in contemporary behavioral genetics (Loehlin, 1992), as well as the fact

that the contributions of genetic and environmental factors to various traits differ across cultures. The aim of our study was to investigate the genetic and environmental contributions to inter-individual variability of personality traits in Russian adolescents and young adults. The sample comprised of 152 monozygotic and dizygotic twin pairs (54% female, 46% male; mean age—18.4 years, SD—3.6 years), residing in Tver', Bishkek, and Izhevsk. The Russian-language version of NEO-PI-R, questionnaire was used as a measure of "Big Five" personality traits (McCrae R.R., Costa P., Martin T.A., Oryol V.E., Rukavishnikov A.A., Senin I.G., Hfebickova M., & Urbanek T., 2004; Orel & Senin, 2008). The model-fitting was used to assess significance of the genetic and environmental factors for each of the five personality traits (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism). The results of model-fitting are following: Openness—47% shared environment, .53% nonshared environment; Conscientiousness—53% additive genetic factors, 47% nonshared environment; Extraversion—44% shared environment, 56% nonshared environment; Agreeableness—50% additive genetic factors, 50% nonshared environment; Neuroticism—59% additive genetic factors, 41% nonshared environment.

The heritability of cluster C personality disorders assessed by both personal interview and questionnaire

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Background: We have previously published the results on genetic and environmental contributions to the 10 personality disorders (PDs) in a population-based cohort of Norwegian twins, based on single-occasion interviews (The Structured Interview for DSM-IV Personality (SIDP-IV)). Heritability estimates spanned from .21 to .38, and the rest of the variance was due to individual-specific environmental factors, with no evidence of shared environmental effects. However, due to time- and instrument-specific measurement error these estimates may be deflated. The heritabilities of cluster A and B PDs have subsequently been estimated combining the interview data with previously obtained self reports based on the Dysfunctional Personality Questionnaire (DPQ). Using measurement models, the PDs were modelled as latent liabilities. The findings from these studies captured substantially higher heritabilities than those based on single-occasion interviews, with estimates ranging from .55 to .72 for cluster A PDs and from .63 to .71 for cluster B PDs. In the current study, we complete our previous findings by estimating the heritabilities of the latent liabilities to DSM-IV cluster C PDs (avoidant PD (AVPD), dependent PD (DEPD) and obsessive–compulsive PD (OCPD)).
Method: The sample includes 2,772 twins (1386 pairs) from The Norwegian Twin Registry born between 1967 and 1979 (mean age at interview 28.1). All subjects had completed both the DPQ containing 91 PD items, and the SIDP-IV. In order to select the DPQ items that best predict the PDs captured by SIDP-IV, we will use stepwise ordinal regression analyses. Subsequently, we will fit biometric measurement models in Mx, where the two PD measurements will be used to model the PDs as latent factors. Results will be presented at the conference.

Assessing physical function in a middle-aged twin cohort

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Numerous studies have reported significant associations between physical function and various age-related traits. The purpose of this study was to: (1) examine genetic and environmental influences on physical function and (2) examine whether physical function is significantly associated with health and psychosocial domains in late midlife.

Analyses included 1237 participants from the Vietnam Era Twin Study of Aging (VETSA). Mean age was 55.4 ± 2.5 (range 51–60). Structural equation modeling (Mx) was utilized to examine associations among four physical function variables (grip strength, rise-from-chair, 10-m walk, and maximum forced expiratory flow).

Factor analysis yielded a single latent factor accounting for approximately 42.6 percent of the variance. The results of the factor analysis were supported by biometrical modeling indicating that genetic and environmental influences for these variables were primarily accounted for by this single "physical function" latent factor. Additive genetic influences explain approximately 50 percent of the variance in the composite variable. Significant associations were observed between physical function and age, smoking, BMI, well-being, education, diabetes, hypertension, and hypercholesterolemia.

Factor analysis and twin modeling identified a single (genetically influenced) 'physical function' factor suggesting that these four biological/health measures may reflect a putative index of biological age. We think it's important to note that physical function was significantly associated with chronological age even in this narrow age range. Physical function also proved to be significantly associated with a wide range of health and psychosocial factors supporting the usefulness of continued research explicating the relationship of physical function to numerous domains of age-related decline.

Examining associations between religious motivation-devotion and heaviness of alcohol consumption: Issues, considerations, and results from a young-adult female twin sample

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Previous research has suggested that high religiosity is protective against alcohol initiation and problem use, but little work has examined associations between religiosity and continuous measures

of alcohol consumption (which are more powerful at detecting small effects than are binary measures). We used data from 3705 individuals who completed the Wave 4 interview and questionnaire assessments for the Missouri Adolescent Female Twin Study (MOAFTS; 1720 complete pairs; 54.4% MZ; M = 21.7 years at interview) to examine overlap between religious motivation-devotion and alcohol consumption. Trivariate genetic models included high religious motivation-devotion (58.9% with a score of 14 or higher on a 6-item measure; M = 13.7, range = 6–18), alcohol use (23.3% less than 6 times lifetime, 13.4% 6–23 times lifetime, 63.3% 24 or more times lifetime), and heaviness of consumption (quartiles from a consumption factor score for those having used alcohol 6 or more times lifetime). Moderate genetic and shared environmental influences were observed for all three measures (motivation-devotion a2 = 0.26, c2 = 0.40; alcohol use a2 = 0.34, c2 = 0.46; heaviness of consumption a2 = 0.40, c2 = 0.28). The genetic correlation between alcohol use and heaviness of consumption was very high (rG = 0.99), but was modest between motivation-devotion and the alcohol measures (rG = −0.25 for alcohol use and rG− = −0.14 for heaviness of consumption). Shared environmental correlations were moderate to high (rC = 0.88 between alcohol use and heaviness of consumption, rC = −0.45 between motivation-devotion and alcohol use, and rC = -0.64 between motivation-devotion and heaviness of consumption). Given the two-stage nature of the two alcohol measures (only those having used alcohol 6 or more times had scores on heaviness of consumption), we conducted sensitivity analyses to address the impact of model misspecification. The present analyses suggest that, in this sample of young adult women, the overlap between religious motivation-devotion and heaviness of alcohol consumption is primarily environmental.

Gene ontology analysis of genome-wide association studies for nicotine dependence

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The identification of the genetic architectures of complex traits, such as Nicotine Dependence, requires the analysis of multiple genetic risk factors [1]. Gene Ontology (GO) analysis exploits the concept that susceptibility alleles for a trait are distributed among sets of genes that share in common biological meaningful characteristics [2]. This approach allows us to examine thousands of putative signals conferring small risk, complementing standard analysis of the top most significant findings [1].

We analyzed two Genome-wide association studies (GWAS): the Australian twin-family study (OZ-GWAS) (1,935 and 2,262 nicotine dependent and controls) and the Study of Addiction: Genetics and Environment (SAGE) (1,294 cases and 2,071 controls). We evaluated the cigarettes per day endophenotype GWAS signals by employing the gene overrepresentation method [2] and gene set enrichment analysis [1], and then selected those terms that were significant in both studies.

We found that several GO terms grouping cholinergic receptors were significant in both studies. Importantly, these terms were also among the most statistically significant ones when we analyzed the Atherosclerosis Risk in Communities GWAS (7221 subjects). We also found other significant GO terms that represent genes involved in the nicotinamide nucleotide metabolic process and regulation of the MAP kinase cascade.

Source code for software developed and reference databases (i.e. ontologies, genome maps, etc.) will be made available at the time of publication.

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Genetically influenced changes in sensation seeking drive the rise of delinquent behavior during adolescence

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Sensation seeking is associated with an increased propensity for delinquency, and emerging research on both personality change and adolescent brain development suggests that mean-levels of sensation seeking increase substantially from childhood to adolescence. The current study tested whether individual differences in the rate of change of sensation seeking predicted within-person change in delinquent behavior, and whether genetically-influenced differences in rate of personality change accounted for this association. Sensation seeking and delinquent behavior were assessed biennially between ages 10–11 and 16–17 in a nationally representative sample of 7,675 youths from the National Longitudinal Study of Youth: Children and Young Adults (CNLSY). Analyses using latent growth curve modeling found that within-person change in sensation seeking was significantly and positively correlated with within-person change in delinquency from childhood to adolescence. Furthermore, behavioral genetic analyses of a subset of 2,562 sibling pairs indicated that there were substantial genetic influences on both initial levels of sensation seeking and change in sensation seeking during early adolescence, with over 90% of individual differences in change due to genetic factors. Finally, these genetically-driven increases in sensation seeking were most important for predicting increases in delinquency, while environmental paths between sensation seeking and delinquency were not significant. These results suggest that developmental changes in delinquent behaviors during adolescence are driven by a genetically governed process of personality change.

Exploring the link between peers and reading performance: Florida twin project on reading

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Purpose: The present study is an examination of the genetic and environmental relationship between antisocial peer behavior and reading performance. It is commonly suggested that peer effects are ideal candidates for identifiable environmental influences on specific cognitive outcomes during development, yet this relationship is not commonly tested in the twin literature. This is especially important to examine in the context of understanding potential causative mechanisms, a technique possible using Direction of Causality modeling within the twin design. *Methods*: Participants included twin's drawn from the Florid Twin Project in Reading (n = 423 twin pairs; mean age = 10.91 years). Each twin completed a questionnaire concerning

the extent to which his or her friends behaved "badly" (M = 1.28, SD = .27, range = 1–3). Twin's reading performance was measured using the FCAT results from statewide testing (M = 334.20, SD = 56.22; range = 100-500). *Results*: A Cholesky decomposition (i.e., no causation but shared covariance) was compared to results from unidirectional and multidimensional causation models. Model comparison tests indicated that the best fitting model was the unidirectional causal model of reading achievement predicting bad peer choice (causal pathway i = .12). *Conclusions*: The model fit indices suggest only a slight difference among the models. However, in the end the best fitting unidirectional model suggests that poor reading performance caused selecting peers who show bad behaviors. Given the high correlation of FCAT scores through the early school years, it can be concluded that poor reading performance during elementary school results in disengagement from school and the selection of antisocial friends during middle school.

Are spouses more genetically similar for attitudes?

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Genetic transmission accounts for a great deal of variation on values, social attitudes and behaviors (Martin et al. 1986; Hatemi et al. 2010). In this way, children resemble their parents largely because of their genetic relatedness, and not simply their social upbringing. Focusing on whom individuals choose to procreate with, and how mate pairs are related, rather than how they raise their children may provide novel pathways for the development of a host of attitudinal and behavioral traits. Among social, behavioral, psychological, or physical traits spouses assort on political predilections more than any other, except religion (Alford et al. 2011; Eaves and Hatemi 2008). Here we explore this relationship by examining whether spouses are more genotypically similar for political preferences. Using a large population of Australian kinships ($\sim$7,000), we conducted GWAS analyses for social attitudes. Then, similar to explorations of schizophrenia (Purcell 2009) we created profile scores using all snps with a p value of $<10 \times 5^{-05}$ with the aim of capturing variance explained by genetic markers with small effects. We then compared a sample of 700 mate pairs to randomly assigned pairings of unrelated individuals within the population and found that the profile scores of spouse pairs are significantly more correlated than those of non spouse pairs. The implications for genetic diversity, attitude polarization, and research will be discussed.

A genetically-informed study of the effect of marital status on depressive symptoms in the MIDUS sample

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Married individuals tend to be happier (Johnson & Wu, 2002; Wade & Pevalin, 2004) and healthier (Umberson et al., 2006). Carr & Springer (2010) report social selection and causation as the two dominant explanations of the marriage benefit. The present study investigates whether the effect of marital status on various indices of psychological health is mediated by genes or shared environment, or whether the non-shared environment (an explanation consistent with a causal effect) is accounting for the relationship. We analyzed 614 same-sex twin pairs (166 F–F MZ pairs; 154 M–M MZ pairs; 179 F–F DZ pairs; 115 M–M DZ pairs) from the National Survey of Midlife Development in the United States Sample (MIDUS; Brim et al., 1995-1996). In men, we found a phenotypic effect of dichotomized marital status (0 = married, 1 = nonmarried) on Major Depressive Disorder diagnosis (b = .630, $p < .05$). In women, we found a phenotypic effect of marital status on positive affect (b = −.163, $p < .01$), negative affect (b = .156, $p < .01$), and psychological well-being (b = −.161, $p < .01$). Power to differentiate the biometric components was limited, but a pattern of nonsignificant trends emerged. For depression diagnosis in males, the nonshared environment appeared to be driving the effect. In females, the nonshared environment was the largest contributor to levels of positive and negative affect, while genetic selection appeared to be involved in the relationship between marital status and scores on the Ryff & Keyes (1995) Psychological Well-Being Scale. Results suggest that marital status is an important predictor of these psychological outcomes, and that the effects of marital status on psychological health may manifest differently in males and females.

The role of assortative mating mechanisms in explaining spouses' marital quality

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Research has demonstrated that genetic influences contribute to the extent of agreement between spouses on their reports on the quality of their marriage (e.g., Spotts et al., 2004), but the potential effects of assortative mating have not been examined. Spouse similarity may be due to phenotypic assortment (i.e., direct selection on phenotypic characteristics) and/or social homogamy (i.e., selection via shared environmental factors, like social background). Using a sample of 909 middle adult same-sex adult monozygotic and dizygotic twin pairs and their spouses from the Twin and Offspring Study in Sweden (TOSS) (Neiderhiser & Lichtenstein, 2007), the present study examined the extent to which mechanisms of assortment contribute to spouse similarity on marital quality. The disentanglement of phenotypic assortment and social homogamy relies primarily on comparing extended family relationships (i.e., similarity of in-laws to one another compared to spouse similarity) (cf. Reynolds, Barlow & Pedersen, 2006). In a model that allowed for phenotypic assortment and social homogamy, results revealed that the process of assortment for marital quality was due to phenotypic assortment. The phenotypic assortment path was 0.57, heritable influences were moderate at 29%, whereas nonshared environmental contributions explained the remaining 71% of the variance in marital quality. Results help to clarify how genetic influences contribute to associations between spouses' marital quality.

Evocative person-environment correlations in mate selection

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According to evolutionary theory, factors that enhance reproductive fitness (e.g., health, personality, status) should largely define one's "mate value." Because many of these traits have genetic underpinnings, examining whether individuals with these traits are indeed perceived to have greater mate value is a first step towards the identification of evocative gene-environment correlations in mate selection. Although prior studies found that individuals report valuing these traits in a potential mate, little to no research has investigated whether or not these traits actually drive mate selection processes. The current study will examine data from a sample of 286 previously unacquainted men and women who were asked to get to know one another in small groups using a speed-dating design. After meeting with each member of the opposite sex, individuals were asked to rate the person on physical attraction and romantic interest. Data will be analyzed using the Social Relations Model in order to capture each individual's overall level of "dateability" or general perceptions of their mate value according to several members of the opposite sex. Individual-level variables (e.g., personality, psychopathology) will be examined in relation to overall dateability in order to explore which characteristics generally increase mate value in the eyes of the opposite sex. In this way, the current study allows for a greater understanding of evocative person-environment correlations in mate selection. Of note, although they are unlikely to be fully analyzed as of June 2011, DNA was also collected from each individual, allowing us to eventually examine whether genes underlie these evocative person-environment correlations (as we hypothesize they would).

Developmental trajectory and environmental moderation of the effect of ALDH2 polymorphism on alcohol use

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Background: In the aldehyde dehydrogenase 2 (ALDH2) gene, the ALDH2*2 allele of the SNP rs671, prevalent in East Asian populations, encodes an enzyme with severely reduced activity, thereby disrupting the normal metabolism of alcohol. Consequently, possession of the ALDH2*2 allele has been repeatedly shown to be associated with lower risk for alcohol dependence, and reduced alcohol use. However, relatively few studies have considered whether the magnitude of the effect of ALDH2 polymorphism upon drinking may be related to developmental stage, or vary by environmental context.
Methods: In a longitudinally assessed sample of 356 adopted adolescents and young adults of East Asian descent, we examined the developmental progression of the relationship between ALDH2 genotype and multiple measures of drinking behavior. We also sought to determine whether the environmental influences of non-biological parent and elder sibling alcohol use, as well as deviant peer behavior, moderated the effect of ALDH2 genotype upon alcohol use.
Results: Across all measures of alcohol use, the association between ALDH2*2 possession and reduced drinking went from insignificant to moderate between mid-adolescence and early adulthood. Adoptive parent and co-sibling drinking consistently moderated the protective effect of the ALDH2*2 allele across measures of quantity and frequency of alcohol use, but not the symptomology or diagnosis of DSM-IV alcohol abuse or dependence. Deviant peer behavior was not consistently related to the effect of ALDH2 genotype.
Conclusions: Results suggest that the relationship between the ALDH2*2 allele and diminished drinking behavior is not uniform, but increases over the course of adolescence and young adulthood, and may be modified by the environmental influence of familial alcohol use.

Twin studies on skin conductance responsiveness

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Little is understood about the psychiatric correlates of skin conductance responsiveness (SCR) and its genetic/environmental structure. In recent years, several large-scale twin studies have amassed a wealth of psychophysiological data in addition to providing comprehensive assessments of personality and behavioral functioning. We discuss some findings on skin conductance responsiveness to repetitive auditory stimuli. Unlike baseline/tonic measures of skin conductance, SCRs to specific stimuli are more clearly influenced by psychological processes such as attention and emotional arousal. As a component of the sympathetic nervous system, SCRs may index an individual's arousability, which in turn may contribute risk for behavioral disinhibition and associated externalizing disorders. Present results are based on 2179 male and female participants of the Minnesota Twin Family Study, all of whom were twins approximately 17 years of age. Of the various SCR measures evaluated, the most consistently heritable across four different age/sex cohorts was response frequency, i.e., the number of trials to which subjects responded electrodermally. Heritability was in the 50–60% range, which is similar to that obtained in another recent study of juvenile twins. SCR frequency explained 2–4% of the variance in a broad factor of externalizing psychopathology. The phenotypic correlations were consistently negative, and most of the overlap was explained by common genetic factors. This suggests that reduced skin conductance responsiveness is a risk factor for externalizing psychopathology. Given its moderate to high heritability, SCR may be a candidate for understanding the etiology of other psychiatric disorders as well.

Accounting for genetic and environmental contributions to associations between negative emotionality and depressive symptoms in adolescence

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Negative emotionality (NE) has been identified as a risk factor for depressive symptoms(DEP). Little, however, is known about the underlying risk mechanism. Is this association based upon experiences that enhance both NE and DEP? Or does this association represent a shared genetic-based risk for NE and DEP? The goal of the present study is to assess the degree to which genetic and environmental factors account for associations between NE and depressive symptoms during adolescence.

Data for this study were from wave 1 of the Nonshared Environment in Adolescent Development(NEAD) project. The sample consisted of a total of 720 families with same-sex sibling pairs between the ages of 10 and 18. Siblings pairs varied in regard to

genetic relatedness, and the sample included monozygotic ($N = 93$), dizygotic ($N = 99$) twin pairs, and full sibling pairs ($N = 95$) from non-divorced families, and full sibling ($N = 182$), half-sibling ($N = 109$), and unrelated sibling ($N = 130$) sibling pairs from step-families. Children's NE and DEP were assessed via the negative emotionality subscales of the EAS Temperament Survey and the depression subscale of the Behavior Problems Index. Mothers, fathers, and children completed both questionnaires. Mothers' and fathers' ratings for both measures were significantly correlated and combined to form composite NE and DEP scales. Analyses indicated that NE and DEP are correlated when different reporters (child vs. parents; r's .17–.22) or the same reporters are used for each construct (r's = .37–.56). In both sets of analyses genetic factors explained most of the covariance between NE and DEP (72% to 100%). Unique genetic and nonshared environmental factors accounted for residual variances in NE and DEP. These findings are consistent with Rothbart and Bates' (1998) contention that genetically influenced characteristics such as heightened NE can predispose children to psychopathology, but do not determine children's developmental outcomes.

Family influences on attitudes and relationships towards pets

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Christy Hoffman; University of Chicago
Terrie Vasilopoulos; University of Chicago
Michael Lyons; Boston University
William Kremen; UC San Diego
Carol Franz; University of California San Diego

There is growing evidence that pet ownership and human-animal interaction (HAI) have positive benefits for human physical and psychological well being. However, there may be pre-existing characteristics related to patterns of pet ownership and interactions with pets that could potentially bias results of research on HAI. This presentation uses data from two studies to examine familial influences on attitudes towards animals, attachment to pet dogs, and frequency of play with pets. In the ongoing Study 1, 94 children and their primary caregivers from 57 families were given self-report measures concerning attitudes towards animals and, among dog-owning families ($N = 20$, 35.1%), relationships with pet dogs. 37 of the 57 families included siblings. Caregivers (93% biological mothers) ranged in age between 29 and 67 (M = 42.1, sd = 7.3); children were aged 10–18 (M = 13.4, sd = 1.7). The correlation between caregivers and children on overall attitudes towards pets was .44 ($N = 43$, $p < .01$), while the correlation for attachment to pet dogs in dog owning families was .36 ($N = 35$, $p < .05$). Sibling pairs did not significantly correlate on either measure (r = .14, $N = 19$, p = ns, for attitudes, r = −.07, $N = 15$, p = n.s., for attachment). In Study 2, 1237 male twins aged 51–60 (M = 55.4, sd = 2.5) from the Vietnam Era Twin Study of Aging answered a single question concerning frequency of play with pets during the past month. Standard univariate twin models revealed significant heritability estimates of .22–.37. While most of the variation was due to nonshared environmental influences (63–71%), shared environmental influences were weak (6–8%) and statistically nonsignificant. Results from these studies provide the first evidence that individual differences in relationships with pets may be influenced by genetic factors. Despite the fact that prior research has shown that childhood exposure to pets is a strong predictor of pet ownership in adulthood, the mechanisms for this are more likely to be through gene-environment correlation, rather than shared environmental influences.

Exploring the dynamic developments of school engagement and achievement in adolescence

Wendy Johnson; University of Edinburgh
Matt McGue; University of Minnesota
William Iacono; University of Minnesota

The personality characteristic of alienation is generally negatively associated with academic achievement in childhood and adolescence. But adolescence is a particularly dynamic developmental period during which alienation increases for many, and both the extent to which achievement is measured and the stakes associated with the measures of achievement increase dramatically during this period. We have little understanding of how the developmental trajectories of alienation and achievement may influence each other, nor of how genetic and environmental influences may be involved in these transactions. In this talk I will report the use of latent change models that make it possible to examine ongoing reciprocal effects of alienation and achievement in participants from the Minnesota Twin Family Study at ages 11, 14, and 17, and their educational attainment at age 25. I will report how the coupling and slope parameters can be decomposed to distinguish genetic from environmental influences and interpret them in the context of gene-environment correlation and interaction. IQ at age 11 will be used as a control variable.

The etiology of stability and change in life events from childhood to adolescence

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Mark Whisman; University of Colorado at Boulder
Robin Corley; University of Colorado
John Hewitt; University of Colorado

Increasing evidence suggests that genes can predispose individuals to experience stressful and negative events, which increase the risk for psychopathology substantially. However, the nature of genetic and environmental influences on life events across development from childhood to adolescence remains unclear. The current study assessed the stability of and change in genetic and environmental influences on negative, dependent life events from age 9 to 16 (assessed annually) in 413 twin pairs from Colorado's Longitudinal Twin Study.

Both the common factor model and the simplex model provided a better fit to the data than the Cholesky model, and the conclusions from these models were similar. Genetic effects were mostly common influences or those carried over from previous ages, rather than age-specific influences. The magnitude of genetic influences increased from age 9 to 12, then remained high throughout adolescence. Conversely, the magnitude of shared environmental influences decreased from age 9 to 12, and remained low throughout adolescence. Finally, nonshared environmental influences were mostly age-specific, and the magnitude of these influences was consistent across ages.

These results are consistent with the literature suggesting that genetically influenced traits and events, such as puberty, depression or neuroticism, may account for the increase in negative, dependent events in adolescence. Increases in the magnitude of genetic influences and decreases in the magnitude of shared environmental influences from childhood to adolescence suggest the possibility of increases in active gene-environment correlation and the importance of social dynamics and relationships outside of the family in adolescence. To our knowledge, this is the first study to document the changes in magnitude of genetic and environmental influences on life

events during the transition from childhood to adolescence. In future research, mediating factors such as personality, psychopathology and cognitive vulnerability should be examined.

Shared environment moderates the heritability of temperament in childhood

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Kathryn Lemery-Chalfant; Arizona State University
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The interplay of genes and environment on children's development is a complex dynamic process. As behavior geneticists begin to model protective as well as risk factors, and interactive as well as main effect influences, development is elucidated. We hypothesized that positive parenting, a quality home environment, and high family cohesion would moderate the heritability of temperament (Children's Behavior Questionnaire—Effortful Control, Negative Affectivity, Extraversion/Surgency). Participants were drawn from the Wisconsin Twin Project and consisted of 1323 twins (51% boys), 88.5% Caucasian, M = 7.93 years (SD = 0.87). Higher order composites for the parenting and family environment moderators were formed from parent reports of Behavior Management Self-Assessment, Child Rearing Practices Report, Family Assessment Device, and Family Conflict Scale. Measures of the home environment (Living Environment Observation Scale and Confusion, Hubbub, and Order Scale) were not composited due to the nature of the variables. Preliminary correlational analyses showed a majority of the temperament and environmental measures to be correlated (r's = .17–.36, $p < .001$). Biometric ACE model fitting suggested the AE model was the best fitting reduced model. For Effortful Control, Negative Affectivity, and Extraversion/Surgency, estimates for the heritability (h2) and nonshared environment (e2) were 0.60 and 0.40, 0.80 and 0.20, and 0.59 and 0.41, respectively. Testing of nested AE moderation models yielded parenting as a significant moderator on the A path for Negative Affectivity, LEOS through the E path for Effortful Control and Extraversion/Surgency, and CHAOS was on the E path for Effortful Control and Extraversion/Surgency. Results suggest that the quality of the environment may act as a permissive or determinative influence on the heritability and expression of temperament. Future analyses include the examination of ADE models. These findings underscore the importance of shared environment, and support the recent literature on the benefits of positive influences on children's development.

Publication bias and false discovery rates in gene-by-environment interaction research in psychiatry

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Gene-by-environment interaction (G × E) studies in psychiatry have typically been conducted in a candidate G × E (cG × E) fashion, analogous to candidate gene association studies on genetic main effects. Such cG × E research has received widespread attention and acclaim, yet cG × E findings remain controversial. We were interested in trying to understand whether the many positive cG × E findings reported in the psychiatric literature were robust or if, in aggregate, cG × E findings were consistent with the existence of publication bias, low power, and a high false discovery rate. We conducted analyses on data extracted from all published studies (to our knowledge, 103 studies) from the first decade (2000–2009) of cG × E research in psychiatry. 96% of novel cG × E studies were significant compared to 27% of replication attempts, findings consistent with the existence of publication bias among novel cG × E studies, making cG × E hypotheses appear more robust than they actually are. There also appears to be publication bias among replication attempts because positive replication attempts had smaller average sample sizes than negative ones. Power calculations using observed sample sizes suggest that cG × E studies are underpowered. Low power along with the likely low prior probability of a given cG × E hypothesis being true suggests that most (e.g. 67%) or even all positive cG × E findings are type I errors. In this new era of big data and small effects, a recalibration of views about 'groundbreaking' findings is necessary. Well-powered, direct replications deserve more attention than novel cG × E findings and indirect replications.

G × E interaction in Drosophila aggressive behavior

Jonathan Arnold; University of Georgia
Andrew Kim; Emory University
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Behavior arises through the interaction of an individual with its environment. An individual has various experiences during its lifetime, and this experience significantly influences subsequent behavior including personality. Aggressive behavior is important for having access to limited resources including mates in nature and has been reported in invertebrates including fruit fly, Drosophila. Molecular studies have identified multiple genes associated with aggressive behavior in Drosophila, and Cyp6a20 gene is significantly associated with aggressive behavior (see Robin et al., 2006; Kim, 2009, for review). Pharmacological studies demonstrate that several neurotransmitters play roles in aggressive behavior (Baier et al., 2002; Dierick and Greenspan, 2007; Johnson et al., 2009). Little is known, however, about the changes in brain function and gene expression in the brain resulting from social experience. In this study we investigated interactions between gene and environment on Drosophila aggressive behavior. Using wildtype and Cyp6a20 mutant flies, D. melanogaster was raised in two different social conditions during development: (1) asocial; and (2) social. We observed aggressive behavior, brain size, and brain protein expression between two types of males. Our data shows that (1) social experience significantly affect aggressive behavior of both types of males: asocial males, regardless of their genotypes, are more aggressive compared to social males; (2) social males express larger mushroom bodies playing roles in olfactory learning and memory; (3) they also express a high level of synaptic proteins which regulate neurotransmitter release in the brains; but (4) when mutant flies are raised in isolation, they are highly aggressive, and their brain size and brain protein levels are more significantly reduced. These results suggest that G × E interaction is one of important mechanisms underlying Drosophila aggressive behavior, which is consistent with human antisocial behavior studies (Caspi et al., 2002; Kim-Cohen et al., 2006; Rice and Thapar, 2009).

Genome-wide association study of general cognitive ability

Robert Kirkpatrick; University of Minnesota
Matthew McGue; University of Minnesota
William Iacono; University of Minnesota

Michael Miller; University of Minnesota
Saonli Basu; University of Minnesota

We will present and discuss results of a first-pass GWAS for cognitive ability, using a sample of $N = 7{,}098$ Caucasian individuals in 2,361 families. This sample combines participants from two longitudinal studies, one of twins and their families and one of adopted siblings and their families. Participants were assessed with an abbreviated version (four subtests) of WAIS-R or WISC-R (as age-appropriate), and were genotyped on the Illumina 660 W Quad SNP chip. In addition, we will present and discuss results of follow-up analyses, including gene-based tests (VEGAS; J. Z. Liu, et al., 2010, American Journal of Human Genetics, 87, 135–149) and plans for analysis of longitudinal IQ data available from the sample.

Genetic and environmental influences in the moment: A twin study of interpersonal processes between mothers and children

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S. Alexandra Burt; Michigan State University

The parent–child relationship is, in part, influenced by the genetic makeup of the child, via evocative rGE (South, et al., 2008; Jaffee, et al., 2004; Neiderhiser, et al., 1999; O'Connor, et al., 1998; Ge, et al., 1996) but is also shaped by the genetically-influenced characteristics of the parent (Prinzie, et al., 2009; Jaffee, et al., 2006; Spinath & O'Connor, 2003). However, little is known about the ways in which these parent and child influences operate on a moment-by-moment basis. Interpersonal theory provides a useful framework from which to examine moment-by-moment shifts in dyadic behavior. Within a given dyad, interpersonal behavior has been found to vary continuously and simultaneously with regard to two orthogonal dimensions of human relationships, namely warmth/affiliation and control/dominance (Sadler, Ethier, Duong, & Woody, 2009). Specifically, the levels of warmth and control exhibited by one member of a dyad during an interaction are thought to both elicit, and be elicited by, their partner's levels of warmth and control (i.e. complementarity; warmth pulls for warmth, while control pulls for submission). Although these processes have been examined across a wide range of dyads, they have not yet been examined within a genetically-informed framework. The current study will do just this in a sample of 300 twin families. We will specifically use a computer joystick to rate videos of mother-twin dyads interacting in real-time (Sadler et al., 2009). This coding scheme yields individual ratings of warmth and control, as well as dyadic ratings of interpersonal complementarity. These ratings can then be compared across zygosity in order to index genetic and environmental contributions to mother–child interpersonal processes "in the moment". In this way, we will be able to examine the moment-by-moment unfolding of genetic and environmental effects within the mother–child relationship.

Transcriptome changes associated with alcohol exposure during synaptogenesis in a mouse model of fetal alcohol spectrum disorders

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Maternal alcohol consumption during pregnancy results in fetal alcohol spectrum disorders (FASD). Despite our increasing knowledge of the magnitude and breadth of abnormalities associated with FASD, little is known about the underlying biological mechanisms. We have established a C57BL/6J mouse model of developmental ethanol exposure that shows FASD-related behavioural phenotypes. In particular, we have shown that that ethanol treatment representing binge-like doses during synaptogenesis (third human trimester equivalent) results in spatial learning and memory deficits in the Barnes maze. Using this model, we have also identified genome-wide changes in brain gene expression associated with neurodevelopmental alcohol exposure, both immediately following treatment (4 h post-injection) as well as long-term changes (postnatal day 60). Differentially-expressed genes were extracted (1.5-fold, FDR < 0.05) and subjected to gene set enrichment analysis using Gene Ontology annotations for biological function, pathway, or interactions. Results revealed that the acute response to ethanol (4 h) included significant alterations in inflammatory, cell survival, and, interestingly, circadian rhythm-associated gene pathways. Long-term, persistent gene expression changes were more subtle but affected a number of pathways with wider biological roles. This included significant disruption of cadherin gene family cell adhesion molecules and neurotransmitter-associated pathways (glutamatergic, GABAergic, and serotonin systems were all identified). These data suggest that immediate cell survival mechanisms may induce long-term changes in critical cell-communication mechanisms, which may mediate the effects of ethanol exposure during synaptogenesis and its effects into early adulthood. These genes and pathways have relevance to FASD pathogenesis, and the identification of genome-wide changes in neurodevelopmental genetic programming may facilitate our understanding of the permanent behavioural and neurocellular consequences of prenatal alcohol exposure.

The effects of puberty on genetic risk for disordered eating: Evidence for a sex difference

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Differences in genetic influences on disordered eating are present across puberty in girls. Heritability is 0% before puberty, but over 50% during and after puberty. Emerging data suggest that these developmental differences may be due to pubertal increases in ovarian hormones. However, a critical piece of evidence is lacking, namely, knowledge of genetic influences on disordered eating across puberty in boys. Boys do not experience increases in ovarian hormones during puberty. Thus, if pubertal increases in genetic effects are present in boys, then factors in addition to ovarian hormones may drive increases in heritability in girls. The current study was the first to examine this possibility in a sample of 914 male and female twins from the Michigan State University Twin Registry. Disordered eating was assessed with the Minnesota Eating Behaviors Survey. Pubertal development was assessed with the Pubertal Development Scale. No significant differences in genetic influences on disordered eating were observed in males across any developmental stage. Heritability was 51% in boys during pre-puberty, puberty, and young adulthood. By contrast, in girls, genetic factors accounted for 0% of the variance in pre-puberty, but 51% of the variance during puberty and beyond. Sex differences in genetic effects were only significant during

pre-puberty, as the best-fitting model constrained heritability to be equal across all males, pubertal females, and young adult females. Results highlight sex-specific effects of puberty on genetic risk for disordered eating and provide indirect evidence of a role for ovarian hormones and/or other female-specific factors.

Variation in the Cannabinoid Receptor Gene (CNR1) and marijuana use: Preliminary data from an experimental study

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John McGeary; Providence VAMC/Brown University

Models that integrate biological and behavioral factors are important to understanding the mechanisms by which genetic variability influences cannabis dependence. The cannabinoid receptor type 1 (CB1), a G-coupled receptor encoded by the CNR1 gene, mediates marijuana's psychoactive effects and rewarding actions. Several polymorphisms in the CNR1 gene have been associated with cannabis dependence and cannabis-related intermediate phenotypes, such as brain response to marijuana cues, but those related to use patterns have been less well characterized. Young adults ($N = 150$, mean age $= 21.6$, SD $= 3.16$) who had used marijuana at least once a week in past month and at least 10 times in past 6 months were recruited for an experimental marijuana administration study (Metrik et al., 2011). Three SNPs in the CNR1 gene were genotyped: rs806368, rs1049353, rs2023239. Associations between CNR1 variation and baseline marijuana use were investigated using PLINK (Purcell et al., 2007). The Time-Line Follow-Back was used to establish a 60-day retrospective marijuana (number of days) baseline. Analyses yielded strong linkage disequilibrium between rs806368 and rs1049353. Twenty percent of the sample possessed the TT haplotype, 21% CC, and 59% TC. Allelic variation across this haplotype was associated with percent marijuana use days (mean $= 41.58$, SD $= 24.28$). Specifically, the TC haplotype predicted increased use and accounted for 3.3% ($p = .0277$) of the variance in marijuana use. These preliminary data suggest that rs1049353 (and haplotypes containing rs0149353) are associated with increased marijuana use. Given the mixed literature of associations of this variant with dependence diagnoses (Benyamini et al., 2011), this finding may suggest differential responses to marijuana's acute effects among frequent marijuana users. Additional replications of associations with indices of marijuana use and cannabis-related intermediate phenotypes such as sensitivity to the acute effects in a controlled marijuana administration laboratory study would provide support for this hypothesis.

Child ADHD: Maternal xenobiotic metabolism genes and smoking during pregnancy

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Sarah Francazio; Providence College
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Maternal smoking during pregnancy (MSDP) is a major public health concern with clearly established consequences to both mother and newborn (e.g., low birth weight, altered cardiorespiratory responses). MSDP has also been associated with higher rates of a variety of poor cognitive and behavioral outcomes in children, including attention deficit hyperactivity disorder (ADHD). However, the evidence suggesting causal effects of MSDP for these outcomes is muddied in the existing literature due to the frequent inability to separate prenatal exposure effects from other confounding environmental and genetic factors. Moreover, specifically considering the genetic influence on the ability of an individual to convert toxic metabolites of cigarette smoke to less harmful ones is important for minimizing other adverse health effects. Using preliminary data from 110 families with full siblings discordant for prenatal tobacco exposure (ages 8–15 years old), we explored the association between MSDP and ADHD-related behavior while also considering the role of two xenobiotic [i.e., corresponding to a chemical compound (such as a drug, pesticide, or carcinogen) that is foreign to a living organism] metabolism genes (CYP1A1 and GSTT1; typed in mothers) in the association between MSDP and child ADHD-related behavior. Results from between-family comparisons of unrelated individuals yield a significant association between maternal GSTT1, but not CYP1A1, and ADHD symptomatology. Moreover, when comparing unrelated exposed children to non-exposed children, results suggest an effect of MSDP on higher ADHD symptomatology. Finally, symptom scores were highest in those children whose mothers smoked during pregnancy and carried the risk GSTT1 genotype. However, when considering full siblings discordant for exposure, the within family MSDP effect was negligible, suggesting that the association between MSDP and ADHD-related behaviors is largely explained by characteristics that are shared between siblings. Moreover, analyses suggest that maternal GSTT1 effects may potentially account for between-family MSDP effects that are seen.

Non-adaptive personality traits and the dark triad: A behaviour genetic investigation into the relationship between the two domains

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Livia Veselka; University of Western Ontario
Julie Aitken Schermer; The University of Western Ontario
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The Schedule for Adaptive and Non-adaptive Personality (SNAP) measures a constellation of 15 traits which capture the extremes of normal personality (Harlon & Clark, 1999). It exhibits a three factor structure similar to the personality structure proposed by Tellegen: Negative Temperament, Positive Temperament, and Disinhibition (Watson & Clark, 2002). The Dark Triad refers to offensive, yet non-pathological personality traits: Narcissism, Machiavellianism, and sub-clinical Psychopathy (Paulhus & Williams, 2002). Although Big Five correlates of the Dark Triad have been examined extensively, the relationship between more extreme personality traits that are not captured by the Big Five and the Triad has not yet been examined. We, thus, conducted an investigation of genetic, common and unique environmental contributions to individual SNAP traits and the Triad facets and their correlations in a twin sample. We observed moderate to strong phenotypic correlations between the total scores on the Triad measures and all the SNAP facets with the exception of workaholism. Univariate behaviour genetic analyses suggested the existence of higher genetic contributions to Psychopathy, Narcissism, and Negative Temperament as compared to Machiavellianism and Positive Temperament. Bivariate behaviour genetic analyses evaluated the

extent of genetic, common and unique environmental contributions to correlations between the non-adaptive personality traits and total scores on the Triad. Genetic correlations between the SNAP facets and Psychopathy and Machiavellianism were found to be stronger than those between the SNAP facets and Narcissism. The opposite pattern was observed for significant non-shared environmental correlations. We review our findings from the perspective of heritability of precursors of sub-clinical offensive personalities.

Scrutinizing the teacher effect using twin methodology

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Robert Plomin

It is commonly believed that children's academic success depends on their teachers to a large extent. In the popular press, as well as in lay discussions, teachers are often blamed for lack of understanding or motivation, or praised for facilitating them. The Teacher Effect is viewed as an overall effect on all children in the class, so that having the same teacher should increase similarity among the children in achievement in the school subject taught by that teacher. Here we report a systematic investigation of the Teacher Effect in the large population-based Twin Early Development Study (TEDS), conducted in the UK. We applied the standard Twin Methodology, comparing MZ and DZ twins' similarity for multiple academically-relevant phenotypes, including cognitive ability, school achievement, and motivational factors collected at 5 assessment points across 7 years of school (age 7 to age 14). These analyses were conducted with an additional comparison—between twins taught by the same teacher vs. those taught by different teachers, estimating the contribution of teachers to the similarity between twins across different ages and different phenotypes. The results showed that the Teacher Effect is not static and varies across ages and phenotypes (e.g., achievement in a subject vs. enjoyment of the subject), as well as a function of the educational setting (e.g., standardized vs. variable curricula). We discuss the absence of the teacher effect for some phenotypes (i.e., no increased similarity for the twins taught by the same teacher) in terms of possible non-shared effects of the teacher, as well as possible teacher effects that do not contribute to the population variance. The results of this systematic investigation have important implications for conceptualizing the Teacher Effect.

Genetic determinants of area patterning in the human cerebral cortex

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Arealization refers to the development of cortical regions leading to differentiation of the cortical primordium into unique areas distinguished by differences in patterns of gene expression, cytoarchitecture, and functional circuitry. Substantial areal expansion of some regions of human neocortex (e.g., prefrontal cortex) is likely important for functional specialization. Experimental animal research aimed at elucidating the genetic determinants of arealization has progressed substantially, yet the genetic underpinnings of cortical area patterning are largely unexplored in humans. There are 2 consistent findings in the mouse brain. First, some specific genes simultaneously cause areal expansion of anterior brain regions and contraction of posterior regions—the anterior-posterior gradient. Second, some genes also expand or contract specific regions resulting in sharply-defined boundaries roughly corresponding to the major lobes. We examined the genetic patterning of cortical arealization in 406 adult twins in the Vietnam Era Twin Study of Aging (VETSA). After adjusting for total surface area, we mapped genetic correlations of cortical area measures between each of 4 selected seed points and all other points on the cortical surface (with no pre-defined regions of interest). Results were consistent with both the anterior-posterior gradient and the sharply-defined boundaries in the mouse brain. Because the observed patterns could have been due to the particular placement of seed points, we next used fuzzy clustering—an agnostic data-driven technique without seed points. When constrained to 2 clusters, we found the same anterior-posterior gradient. The clustering algorithm reached an asymptote at 12 clusters. These were 12 genetically-driven cortical regions maximizing genetic correlations within clusters and minimizing them between clusters. Clusters were always very similar in the left and right hemispheres. Results suggest that the genetic underpinnings of cortical arealization patterns in humans are similar to that of other mammals. Our genetically-based regions may constitute novel phenotypes for imaging genetics studies.

The effects of marriage on alcohol consumption in emerging adulthood: A longitudinal sibling-comparison design

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Background: The transition into marriage is a robust predictor of decreased alcohol consumption in young adulthood; however, studies testing a causal relationship between marriage and reduced alcohol use must contend with selection factors that may account for this relationship. In addition, there is less consistency regarding the potential moderating effects of age at marriage and family history of alcoholism.
Methods: The current study used latent growth modeling to examine associations between marital status and alcohol use, assessed annually in a sample of 10,450 young adults (ages 18–24) drawn from the National Longitudinal Survey of Youth. A sibling-comparison design was used to control for family-level environmental and genetic background factors that may have influenced both likelihood of marriage and alcohol consumption, as well as an individual's previous trajectory of alcohol use. A multiple group design was used to examine whether family history of alcoholism moderated the effect of marriage on alcohol use.
Results: Results showed that after controlling for between-family differences, getting married was associated with a decrease of 5.66 drinks per month. Neither age at marriage nor parental alcoholism moderated this effect.
Conclusions: These findings are consistent with research showing that trajectories of alcohol consumption in emerging adulthood are altered at marriage. Results of within- and between-family analyses suggest a causal relationship between marriage and decreased alcohol

consumption rather than an association due to unmeasured selection factors. These findings suggest that, among young adults, getting married may serve as a protective factor against heavy alcohol consumption, even for individuals who marry relatively early. Further research on the relationship between substance use and other transitions in young adulthood (i.e. parenthood, employment) may also benefit from the sibling comparison design as a way to test causal environmental hypotheses.

Advancing paternal age and offspring violent criminality

Ralf Kuja-Halkola; Karolinska Institutet

Advancing paternal age has been identified as a risk factor for schizophrenia, bipolar disorder and autism spectrum disorder. Up to date, there are no studies on the possible effect of advancing paternal age on criminality.

Using total Swedish populations data, we identified 2,359,921 individuals in 1,289,735 families born in 1958 through 1979. We used the National Crime Registry to identify all violent criminal convictions (1973–2005). To control for possible genetic and/or shared environmental confounding of the association between advancing paternal age and offspring criminality we tested within family effects (i.e., within siblings who differed in paternal age at childbirth). We used generalized estimation equations to study the probability for an individual to ever be convicted of a violent crime and the rate of violent offenses in individuals who were convicted at least once.

We identified 95,127 individuals who were registered of committing 240,699 violent crimes. We found an association between advancing paternal age and offspring violent offending which persisted when controlling for risk factors and familial confounding. Within siblings the one with older father at childbirth has a higher risk for being convicted of violent crimes.

Thus, it seems as the paternal age effect detected among severe psychiatric disorders is also a risk factor for violent criminality. A possible mechanism is de novo-mutations in the male germ-line.

Familial aggregation of sexual offending: Total population study of 21,000 convicted men 1973–2009

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Background: Violent antisocial behaviour is aggregated in families; having a violent relative substantially increases an individual's own likelihood of being violent. However, specifically for sexual offending, essentially nothing is known about familial aggregation and its genetic and early environmental determinants.
Method: We investigated all convictions for sexual crime in Sweden 1973–2009 among more than 13.5 million individuals in the nationwide Multi-Generation Register. Using a nested case–control design, we compared rates of sexual offense convictions (from age 15 and up; National Crime Register) among relatives of sexual offenders with those among relatives of matched (by gender and age of proband and relative), sexually non-convicted controls. Since <1% of convicted sex offenders were female, only male offender probands and male 1st degree (fathers and brothers) and 2nd degree (half-brothers) relatives were studied. We investigated familial aggregation of any sexual offence ($N = 21{,}566$), rape against an adult ($N = 6{,}131$) and child molestation ($N = 4{,}465$). Heritability estimates were obtained from generalized linear mixed models with a probit link.
Results: We found strong familial aggregation of sexual offending among 1st degree relatives [e.g. matched odds ratio (OR) for brothers = 5.1, 95% confidence interval (CI) 4.5–5.9], lower for 2nd degree relatives [e.g. $OR_{maternal}$ half-brothers = 1.7, 95% CI 1.2–2.4]. There were also crime-specific effects [e.g. $OR_{brother}$ for rape = 17.4, 95% CI 11.9–25.4], suggesting both general and subtype-specific familial risk factors for sexual offending. The pattern of relative risks across relations provided evidence for both genetic and non-shared environmental influences on the liability of sexually violent behavior. Specifically, the heritability estimate for the liability of any sexual offending was A = 40% (C = 2%), somewhat lower than previously reported for non-sexual violent crime.
Conclusions: Our findings suggest that familiality should be accounted for in etiological research on sexual offending, prevention efforts, and applied violence risk assessment among convicted sexual offenders.

The association between low birth weight and ADHD symptoms: A co-twin control design

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Objective: Studies have found associations between low birth weight and ADHD. However, this association could be due to familial confounding. Our objective was to investigate whether birth weight affect the risk of ADHD in childhood, controlling for shared environment and genetic factors.
Methods: Parents of all Swedish 9- and 12-year-old twins born between 1992 and 2000 were interviewed for DSM-IV ADHD symptoms. Birth weight was collected prospectively through the Medical Birth Register. We used both a dichotomous approach for birth weight and ADHD and continuous measures to investigate between- and within-twin pair effects.
Results: Our results showed that birth weight of <2,500 g was associated with an increased risk for the inattentive component of ADHD (OR = 1.69; 95% CI: 1.38–2.06), but not the hyperactive-impulsive component (OR = 1.01; 95% CI: 0.78–1.32). In the co-twin control analyses, birth weight of <2,500 g was significantly related to an increased risk of inattention symptoms among differentially exposed monozygotic twin pairs (OR = 3.67; 95% CI: 1.02–13.14).
Conclusions: There is an association between low birth weight and the inattentive component of DSM-IV ADHD independent of shared (familial) environment and genetic factors. Thus, fetal growth restriction seems to represent a modest but fairly consistent environmental influence on the development of ADHD symptoms.

Gene-environment interaction in the development of substance use and related behaviors: Initial analyses from the GENI Project

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Submitted as part of symposium: Gene-Environment Interaction in Substance Use and Externalizing Behavior: Taking Genetic Research to Minority Populations and Rethinking Our Models

In recent years, several genes have been identified as strong candidates for one or more substance use disorders (e.g., alcohol, illicit drugs) in adulthood. Moreover, many of these same genes have demonstrated robust associations with more general externalizing-spectrum behavior(s) during earlier periods of development. Further, these associations have been shown to vary as a function of environmental features, such as parental monitoring and peer deviance. Initial analyses conducted on the GENI sample focus on the role of three genes/gene complexes (GABRA2, CHRM2, DRD2/ANKK1) in the development of risk across and within discrete domains of externalizing behavior (e.g., substance use, HIV risk taking, and disruptive behavior disorders), wherein developmental models are utilized to exploit the cohort-sequential, longitudinal nature of the phenotypic data. In addition to testing for main effects of these genes in relation to externalizing behavior(s), we further examine the extent to which the magnitude of said effects depends on characteristics of the environment. We focus both on environments that have been widely studied in the literature (e.g., parental monitoring), as well as those which may be particularly salient within populations like those represented by the GENI sample (e.g., neighborhood ecology). In this way, we aim to extend models of gene-environment interaction to understand the development of substance use problems across different cultural and socioeconomic groups.

Quadratic COMT × Sex predicts anxiety and depression in middle childhood

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Anxiety and depression are common, moderately heritable psychiatric disorders that negatively impact quality of life. COMT is a key enzyme in the breakdown of dopamine in the prefrontal cortex. Dopamine is critical for modulating cognitive functioning, which impacts behavior, thoughts, and emotions. Importantly, the association is U-shaped, with too little or too much dopamine having deleterious effects. In addition, mouse studies suggest that COMT enzyme activity is sexually dimorphic. The COMT gene has a common functional di-allelic polymorphism (val158met) with codominant alleles, each having environmental specific selective advantages. We tested for linear and quadratic associations, and moderation by sex when predicting childhood depression and anxiety. The sample comprised 762 twin children (95% Caucasian; 49.8% female; M age = 7.1 years; 199 met/met, 369 val/met, and 194 val/val for rs 4680) participating in the Wisconsin Twin Project. Internalizing symptoms were assessed with the Diagnostic Interview Schedule for Children (DISC-IV), and mother and father reports on the Child Depression Inventory (CDI) and the Health and Behavior Questionnaire (HBQ). Using multilevel regression, results supported sexually dimorphic, quadratic effects of COMT on childhood depression and anxiety. Specifically, quadratic COMT × sex predicted DISC-IV depression ($p = .008$), DISV-IV generalized anxiety ($p = .063$), DISC-IV separation anxiety ($p = .017$), mother report CDI depression ($p = .054$), father report CDI depression ($p = .042$), mother report HBQ depression ($p = .036$), mother report HBQ overanxious ($p = .016$), mother report HBQ separation anxiety ($p = .002$), and father report HBQ separation anxiety ($p = .012$). The direction of effects was consistent, with the quadratic effect of COMT significant for boys but not girls, and those carrying the protective val158 having less anxiety and depression. These results underscore the role of COMT for childhood internalizing problems and the need to model nonlinear associations.

fMRI study in identical twin pairs discordant for regular smoking

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Context: Despite the tremendous public health and financial burden of cigarette smoking, relatively little is understood about brain mechanisms that subserve smoking behavior.
Objective: To investigate the effect of lifetime regular smoking on brain processing in a reward guessing task using functional magnetic resonance imaging (fMRI).
Design: A co-twin control study design in monozygotic (MZ) twin pairs.
Setting: Research volunteers from a female twin sample representative of the state of Missouri.
Participants: Young adult (24–34 years) MZ twin pairs ($n = 15$ pairs), discordant for lifetime regular smoking, but concordant for having ever tried smoking cigarettes. Twins were recruited from a population-based sample of female twins. Both twins of a pair had to be willing and eligible to participate. Exclusion criteria included heavy use of alcohol or illicit drugs, neurological problems, claustrophobia, presence of metal in the body, or pregnancy.
Main Outcome Measure: Brain activation differences in response to winning or losing money between twins reporting history of regular smoking and their co-twin sisters who never smoked regularly.
Results: We identified one set of bilateral reward-processing regions (caudate, anterior and posterior cingulate, medial frontal and parietal cortex, insula) that showed activation differences in response to winning or losing money but no significant effect of regular smoking; and a second (non-overlapping) set of frontal/parietal regions, predominantly in the right hemisphere, that showed larger activation in regular smokers compared to their never-regular smoking twin sisters but no effect of winning or losing money.
Conclusions: Considering that the regular smoking twins were overall light smokers, the results suggest that frontal/parietal cognitive control systems are significantly altered at low smoking levels, while reward-processing systems are not.

Understanding the genetic bases of religious belief: Heritable bases of religion can be explained by pre-existing mechanisms underlying social integration and existential uncertainty

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Recent research has demonstrated that religious belief contains a genetic component. Understanding the mechanisms underlying this heritable influence on religiosity will be important in understanding the functions of belief. Here we test a theory that genetic influences on religiosity reflect broader constructs of need for meaning and desire for social integration. In almost 1000 twin pairs, genetic influences on existential uncertainty and social integration completely

accounted for the genetic effects on religiosity. The remaining variance in religiosity reflected family and individual environmental influences. These findings suggest that religion reuses systems involved in meeting basic social and existential needs, and highlight the additional role of cultural transmission in shaping religious belief. We discuss the idea that religious behaviour may reflect, in part, the activity of mechanisms designed to enhance social cohesion. A testable prediction is that other systems meeting these needs will act as substitute goods for religion.

A sample of male–male twin pairs indicates genetic overlap in the causes of hypertension and panic attacks

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Panic disorder has been associated with increased risk of vascular and coronary artery diseases. One possible connection between vascular health and panic disorder is the elevated rates of hypertension observed in panic disorder patients and vice versa. In fact, patients with panic disorder have been used as models for the role of anxiety in the development of hypertension, and elevated cortisol and Phenylethanolamine *N*-methyltransferase (PMNT) levels have been identified in both (Esler et al. 2008a, b). We used a sample of 1,874 monozygotic and 1,485 dizygotic male–male Vietnam-Era veteran twin pairs to explore underlying determinants of panic attacks (an essential feature of panic disorder) and self-reported hypertension (ages 30–48). We examined several genetic models that allow for correlation of underlying genetic liability to these two traits. Consistent with previous literature, we found a higher rate of hypertension for those with panic attacks (OR = 1.7, 95% CI = 1.3–2.2) and that both traits are moderately heritable (.35 heritability in panic attacks and .50 in hypertension). Additionally, we found a genetic correlation (r = .42, 95% CI = .25–.66) between the genetic liabilities of these two outcomes. These models indicate overlapping genetic influences are the source of the elevated comorbidity observed in panic attacks and hypertension. Although these results need to be confirmed in samples that include women and direct measurements of blood pressure, they suggest that caution is appropriate before using panic disorder patients as models for the role of anxiety in causing hypertension. Shared genetic liability for both conditions, rather than a causal effect of anxiety on blood pressure, is most consistent with our data. These results may also be informative for genetic studies of panic. That is, rare genetic variants in vascular-related genes identified in next-generation sequencing of panic-rich families may be interesting candidates for both panic disorder and hypertension susceptibility.

Gene–environment interactions predict parent-rated delinquency

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This study examined genetic and environmental influences on aggression and delinquency in children and adolescents. Although research has implicated longer repeats of the DRD4 polymorphism and the A1 allele of the DRD2 polymorphism in placing individuals at greater risk for a number of adverse outcomes, including novelty seeking, attention problems, and aggression, findings have been inconsistent. The present study hypothesized that youth with dopamine receptor (DRD2 and DRD4) risk alleles and delinquent peers or siblings would engage in increased externalizing behaviors at follow-up. The sample consisted of 58 twin pairs, aged six to 16 (mean age = 8.78 years), who originally participated in the Southern Illinois Twins and Siblings Study at age five. Heritability was significant for age 5 parent-rated aggression (h2 = .85) and was marginal for age 5 parent-reported delinquency (h2 = .63). However, these behaviors at follow-up were not significantly heritable. To explore adolescent delinquency further, a moderator model was tested with multiple regression analyses to examine additional environmental factors and specific genetic mechanisms that may account for these behaviors. DRD2 significantly predicted parent-reported delinquency at follow-up, and there were significant interactions between delinquent peers and both DRD2 and DRD4. Explicitly, those youth with more delinquent peers and with the DRD2 risk allele engaged in more delinquent behavior. In contrast, those with more delinquent peers and the DRD4 non-risk allele engaged in more parent-reported delinquent behavior. However, only number of delinquent peers significantly predicted self-reported delinquency at follow-up. These findings suggest that genetics and biological factors are important to consider in the development of externalizing behavior, but they also underline important differences between youth and parent ratings of delinquent behavior.

Differential associations of MAOA and 5-HTTLPR with reactive and proactive Aggression

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Two of the most heavily studied genetic markers in association with aggression in humans are a variable number of tandem repeats sequence (VNTR) in the promoter region of the gene coding for monoamine oxidase A (MAOA) and the serotonin transporter linked-polymorphic region (5-HTTLPR) of the serotonin transporter gene, both of which have been associated with activity in brain regions such as the amygdala and prefrontal cortex. Though aggression has been defined and studied in a variety of ways, one common strategy among researchers is to classify different types of aggressive behavior into more specific subcategories, such as reactive aggression and proactive aggression. However, in genetic research on aggression, few studies have compared these two markers' association with both reactive and proactive aggression in the same sample. In a sample of 341 children, we collected genetic information for MAOA and 5-HTTLPR, as well as mother's rating of their reactive and proactive aggression. We found a significant association between the low activity MAOA allele and reactive aggression when controlling for 5HTTLPR, but no association between MAOA and proactive aggression, nor an association between 5-HTTLPR and either form of aggression. These findings confirm that MAOA seems to be associated with reactive aggression specifically, especially when its effects are isolated from the influence of other markers. More generally, these results suggest that aggression researchers should focus on determining more specific forms of behavior under genetic influence, while also attempting to test the unique effects of each marker by holding other markers with similar areas of expression constant.

Data-mining genome-wide data: A comparison to conventional GWAS

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Conventional GWA studies are often underpowered to detect true positives due to small effect sizes and the need for multiple testing corrections to prevent acceptance of false positives. While recent meta-analyses have produced replicated associations for some phenotypes, the results in terms of explained variance have not solved the hidden heritability problem. Statistical learning methods such as Random Forest (RF) have been proposed as an alternative to conventional GWAS. We developed methods that solve LD and MAF induced bias of the variable importance measures commonly used in RF and Gradient Boosting Machine (GBM). Since the methods also provide a drastic reduction in parallel computation time, RF and GBM are computationally feasible for large imputed data sets. We present a comparison of RF, GBM, and conventional GWAS using MDD, height, and hair morphology as phenotypes.

A behavioral genetic study of sub-clinical personality disorders and trait emotional intelligence

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The present study is a behavioral genetic investigation of relationships between sub-clinical personality disorders and trait emotional intelligence (TEI). Four subclinical personality disorders were identified using the Schedule for Nonadaptive and Adaptive Personality (SNAP; Harlan & Clark, 1999): Avoidant Personality Disorder (APD), Borderline Personality Disorder (BPD), Obsessive Compulsive Personality Disorder (OCPD), and Schizotypal Personality Disorder (SPD). Research attempting to identify personality traits that may uniquely define subclinical levels of Axis II disorders has found support for the use of the SNAP in identifying personality traits associated with these disorders in both clinical (Morey et al., 2003) and nonclinical (Wilt, Schalet, & Durbin, 2010) samples. Behavior patterns typical of individuals with personality disorders are associated with considerable personal and social disruption. Trait emotional intelligence, which is defined as an individual's self-perception of their emotional abilities, may be particularly impaired in individuals high on personality traits associated with these personality disorders. Trait EI has recently been linked to the Dark Triad of Personality, a collection of subclinical socially aversive traits, with the finding that EI is negatively associated with psychopathy and Machiavellianism and positively related to Narcisssim (Petrides, Vernon, Schermer, & Veselka, 2011). As trait EI reflects an individual's self-perceptions of their emotional abilities, it is expected that trait EI will be negatively related to APD, BPD, and SPD in particular, as these personality disorders are characterized by instabilities in moods, eccentric thoughts, and avoidance of social interactions. Preliminary analyses identified negative correlations between trait EI and APD, BPD, and SPD and a positive correlation between OCPD and trait EI. Univariate and bivariate behavior genetic analyses will be conducted to examine the extent to which genetic, common and unique environmental factors contribute to the phenotypic correlations between subclinical PDs and trait EI.

Which heritability estimates of smoking progression measures are the most accurate?

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Background: Numerous twin and family studies have reported significant genetic contributions to the variability of smoking behavior. However, the range of heritability estimates is quite large. This is partly due to the variety of measures used to describe dependency on nicotine, and partly to the discrepancy in the methods used to estimate heritability.
Methods: We used structural equation modeling to compare heritability estimates obtained using univariate twin analyses versus a multi-step conditional approach which corrects for the conditionality of smoking progression on smoking initiation. The tobacco variables were assessed by personal interview in female, male and opposite-sex twin pairs from the population-based Virginia Twin Registry.
Results: The results suggested that the heritability estimates differed significantly by method of analysis. When smoking progression variables are analyzed with traditional univariate genetic analyses, estimates vary by whether non-smokers are excluded from the analyses or included by assigning zero values to them. Furthermore, both sets of results vary from bivariate analyses which take the conditionality of smoking initiation into account and allow for the correlation between initiation and progression to be estimated. More importantly, the order of variables by degree of heritability of different progression measures varies according to method of analysis, and the amount of genetic overlap between initiation and progression.
Conclusions: This study showed that estimates of heritability of smoking progression measures may be biased by the method of analysis.

Do different types of perinatal risk differentially mediate associations between genetic risk for psychopathology and infant behavior?

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Multiple perinatal risk factors are associated with child mental health problems (i.e. stress, depression, infection, drug use; e.g. Allen et al., 1998; Wadhwa et al., 2001). Perinatal risk (PR) is one mechanism for inter-generational transmission of genetic influences on risk for psychopathology (gRFP). Using the Early Growth and Development adoption study, we tested how different types of PR differentially mediated associations between gRFP and infant behaviors.

Composite anxiety/depression and externalizing/substance use variables were created as a measured proxy for gRFP (Substance Use: Andrews & Peters, 1998; Anxiety/Depression: Beck et al., 1993; Externalizing: Elliot & Huizinga, 1993). Six indexes of PR (total Obstetric Complications [OC], Pregnancy Complications [PC], Neonatal Complications, Drug Use, Exposure to Toxins, and Anxiety/Depression) were created based on the McNeil-Sjostrom Scale for Obstetric Complications (McNeil et al., 1994). Child challenging behavior, fussy-difficult behavior, and unresponsiveness were

measured by the higher score of adoptive mother and father report (Bates et al., 1979; Crnic & Greenberg, 1990; Olson et al., 1982; Rothbart, 1994; Seifer et al., 1996). We fit a series of path models to determine associations between measured gRFP, PR, and child outcomes for each PR type.

Different types of PR were associated to varying degrees, and the vast majority of birth mothers experienced some form of risk during pregnancy (Table 1). Associations between gRFP and PR differed by type of PR as did associations between PR and child outcomes (Fig. 1). Different birth mother characteristics were related to discrete types of prenatal risk. There was limited differential prediction by risk type: PR was generally associated with under-arousal.

Shared environmental influences on personality: Is the effect different depending on method?

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Twin studies of personality consistently show that genes are an important influence and that, surprisingly, shared environmental influences are not (as evidenced by near-zero estimates of c2; e.g., Bouchard & McGue, 2003; Loehlin, McCrae, Costa, & John, 1998). Another way of investigating the etiology of personality is to compare similarity among family members who are biologically related and those who are adopted. The adoption design is more powerful than twin designs are in elucidating shared environmental effects because it allows direct examination of the influence of the rearing environment (i.e., the correlation among unrelated relatives living together), and thus could lead to different estimates of c2. Recently, Burt (2009) published a meta-analysis of twin and adoption studies examining psychopathology; she found that, despite previous consensus that c2 played a minor role in the development of most disorders, it could actually explain 10–19% of the variance in specific internalizing and externalizing disorders. It is possible that inclusion of a large number of adoption studies contributed to this finding. It is thus important to determine whether shared environmental influences on personality have been underestimated by the overrepresentation of twin studies in the literature. The present study compares estimates of shared environmental influence on personality gleaned from twins and from adoptive family members from the Minnesota Center of Twin and Family Research. Results are forthcoming.

Twenty-one year weight change in Vietnam-era twins: Effects of genetics and frequency of contact

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Background: Recent research highlights the importance of social influences on weight change over time. Weight change is also well known to be heritable. We examined whether frequency of contact between members of a twin pair is associated with similarity in weight change from young adulthood to middle age, independent of genetic influences. *Methods*: Participants were 1966 monozygotic and 1529 dizygotic male twin pairs who had height and weight measured at military induction (mean age = 19.69, SD = 1.60, modal year of induction 1968) and reported on their height and weight in 1990 (mean age = 40.77, SD = 2.91). Twin structural modeling (Mx) was used to determine the amount of variance in change in body mass index (BMI) attributable to social contact when genetic and shared environmental effects were taken into account. Social contact was represented by a latent variable that varied by the average report of social contact for each twin pair (Mazzeo et al., 2010). *Results*: Over the 21 year interval, participants gained on average 29.21 lbs (SD = 22.18) with a mean BMI change of 3.31 kg/m^2 (SD = 3.19). As expected, monozygotic twins showed greater similarity in BMI change than dizygotic twins ($p < 0.01$) and also reported more social contact ($p < 0.001$). In twin modeling, social contact accounted for 16% of the variance ($p < 0.001$), in addition to significant additive genetic (42%) and nonshared environmental effects (41%). *Conclusions*: These results document both genetic AND social influences on weight change over young adulthood.

Predictors of relapse in a bupropion trial for smoking cessation in recently-abstinent alcoholics: Preliminary results using an aggregate genetic risk score

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Rates of smoking in the U.S. population have decreased overall, but rates in some groups, including alcoholic smokers, remain high. Many newly sober alcoholics are concerned about their smoking and some attempt to quit. However, quit rates in this population are low. Prior studies suggest risk for relapse in this population may be genetically influenced and that genetic factors may moderate response to treatment. In this exploratory study, we had two specific aims: (1) to investigate associations between genetic risk and outcome; (2) to investigate whether genetic risk moderates the efficacy of a medication intervention. Data are from a subsample of 90 participants from a clinical trial of smoking cessation treatment for smokers with between 2 and 12 months of alcohol abstinence. Subjects were randomly assigned to bupropion or placebo. All subjects received counseling and nicotine patches. To examine the possibility that bupropion may have been efficacious in participants with a specific genetic profile (i.e., a pharmacogenetic approach), an aggregate genetic risk score was created by combining risk genotypes previously identified in bupropion treatment studies. Although medication efficacy was not moderated by the aggregate genetic risk score, there was an interaction between nicotine dependence, and genetic risk in predicting smoking abstinence rates at the end of treatment (10 weeks). Results suggest an aggregate genetic risk score approach may have utility in treatment trials of alcoholics who smoke. Additionally, these findings suggest a strategy for understanding and interpreting conflicting results for single genetic markers examined as moderators of smoking cessation treatment.

A Genome-Wide Association Study (GWAS) of behavioral disinhibition

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As part of the Genes, Environment and Development Initiative (GEDI), 8405 participants in longitudinal research at the Minnesota Center for Twin and Family Research (MCTFR) have been genotyped on Illumina's 660W quad array. Restricting our analysis to individuals of European ancestry ($N = 7702$), we report findings from a GWAS on multiple indicators of behavioral disinhibition. Specifically, using a Rapid Feasible Generalized Least Squares (RFLGS) approach to control for familial clustering in the MCTFR sample (Li et al., in press), we report results for a genome scan of the following dimensional indicators of behavioral disinhibition (Hicks et al., in press): Nicotine, Alcohol Use, Alcohol Dependence, Illicit Drugs, and Behavioral Disinhibition. We report GWAS results for each component phenotype as well as for an omnibus multivariate test. We also evaluate evidence for relevant candidate genes using the VEGAS approach (Liu et al., 2010) and top SNP hits from other relevant GWAS. Findings are interpreted within the context of the overall aims of GEDI—to characterize gene-environment interplay in the development of substance use disorders.

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ENIGMA, enabling neuroImaging genetics through meta-analysis: Progress six months in

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In the genetic dissection of the brain, genome-wide association scanning (GWAS) will be a powerful tool. It is possible that some brain imaging phenotypes are closer to the site of gene action, and that therefore some large gene effects may be found with relatively small sample sizes. However, it is more likely that, as for other complex phenotypes so far investigated, most brain phenotypes will be highly polygenic, most gene effect sizes will be small, and very large numbers of subjects will need to be MRI and GWAS scanned to detect significant gene effects. Both these activities are very expensive and any one lab is unlikely to be able to collect a sufficient sample by itself. To this end we have formed the ENIGMA (Enabling NeuroImaging Genetics through Meta-Analysis) consortium to bring together research groups collecting MRI phenotypes and GWAS. In addition to all the usual problems in conducting GWAS meta-analysis for standard phenotypes, MRI phenotypes present special problems in standardization of measurement and, for voxel-wise measurement, a huge problem in multiple testing, with hundreds of thousands of voxels measured typed for millions of SNPs. These problems will be discussed and early results from the ENIGMA consortium will be presented.

Multivariate cholesky model of early family environment, sexual maturity, and sexual activity in females

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Several studies have indicated that females who reach sexual maturity earlier tend to engage in sexual activity earlier, and many studies have established links between early father absence and both precocious menarche and sexual activity for daughters. Some studies have indicated the relationship between father absence and daughter's sexual activity is only due to its relationship with menarchal timing, while others argue the relationship is due to selection forces. The current study uses data from the NLSY79 in a genetically informed Cholesky ACE model to evaluate the possible links between father absence, age of menarche, and age of first intercourse to establish the relative influence of genetics and early common environment on these outcomes, and to assess whether common or separate sources of variance underlie these outcomes. Unlike father absence measures used in some previous research, our sample allows us to use a continuous measure of the father's presence from birth to age seven, the "critical period" of father influence on sexual variables identified by previous research. While age of menarche shows the expected genetic influence, our results also suggest a common environmental source of variance underlying both father presence and age of first intercourse together, while a second, possibly later environmental source affects the timing of first sexual intercourse independent of father presence.

Stressful life events moderate genetic and environmental influences on adolescent externalizing behavior

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Adolescence is a period in which life can become increasing stressful and uncertain, as youths are confronted with a multitude of changes and transitions involving work, school, and living situations. High rates of behavior problems and other externalizing spectrum disorders, including alcohol use, are observed in adolescence. Several longitudinal studies have indicated that major life events and daily

hassles are prospective predictors of adolescents' emotional and behavioral functioning. As there appears to be converging evidence from psychology, neurobiology, molecular genetics and twin epidemiology that stressful life events interact with genetic predispositions to produce negative outcomes in adolescence, we explored this relationship in the present twin study. The present study uses data from a sample of Finnish twins ($n = 4{,}594$) to examine the moderating effects of the number of stressful life events on the genetic and environmental influences on behavior problems and alcohol use at age 14. Greater stressful life events scores were positively and significantly correlated with behavior problems at age 14 and frequency of alcohol use at age 14. There was a significant main effect of the number of stressful life events on age 14 behavior problems ($\chi2 = 38.52$, DF = 1, $p < 0.00$). A greater number of stressful life events were associated with more behavior problems. Similar effects were observed with age 14 alcohol use; a significant main effect of the number stressful life events on age 14 alcohol use frequency ($\chi2 = 42.28$, DF = 1, $p < 0.00$). The importance of both additive genetics and the environment change as a function of the number of stressful life events ([A] $\chi2 = 14.0$, DF = 1, $p < 0.00$; [C] $\chi2 = 12.27$, DF = 1, $p < 0.00$; [E] $\chi2 = 22.0$, DF = 1, $p < 0.00$). In the conditions of more stressful life events, both additive genetics and shared environment play a more important role; conversely, in the conditions of less stressful life events, latent genetic factors and shared environmental factors are attenuated.

DRD2 has both trait-specific and general association with multiple measures of alcohol use and abuse

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Alcohol consumption and related problems are a multi-faceted set of complex behaviors. Multivariate analyses of twin and family data a genetic architecture with many different genetic factors influencing various aspects of current alcohol consumption and problems. Prior analyses conducted within the Finnish population-based twin sample, Finntwin16 ($n = 5{,}238$), yielded a twin model suggesting four latent genetic factors that account for the genetic variance across seven measures of alcohol consumption (frequency of drinking, frequency × quantity, frequency of heavy drinking, frequency of intoxication, and maximum drinks in a 24 h period) and two measures of problems (The Rutgers Alcohol Problem Index and The Mälmö-modified Michigan Alcohol Screen Test—MmMAST). The first two latent genetic factors loaded onto all of the drinking measures; the third latent genetic factor loaded exclusively onto maximum drinks in a 24 h period and The MmMAST; and the fourth latent genetic factor loaded onto the two indices of problems. The present study follows up on the complex genetic architecture seen across these measures in the twin analysis with measured genotypic data collected on a subset of 600 individuals from this twin sample. We conducted a series of genetic association analyses across nine Dopamine Receptor D2 (DRD2) SNPs testing the relationship between alcohol use/abuse candidate gene DRD2 and the four latent genetic factor scores provided by the previously indicated twin model. The results follow the model implicated by prior twin analyses, where some SNPs (e.g., rs4245149) are significantly associated across all of the genetic factor scores (p-values = 0.009–0.02), but most significantly associated with the general latent genetic factor score which loads onto all drinking measures ($p = 0.009$), while other SNPs (e.g. rs1799978) are only associated with specific genetic factors, in this case the genetic factor which loads uniquely onto maximum drinks in a 24 h period and the MmMAST($p = 0.008$).

GEDI G × E GWAS: Methods for detecting genotype-by-environment effects in full genome scans

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Saonli Basu; University of Minnesota
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The detection of genotype-by-environment (G × E) interaction effects in substance use and behavioral disinhibition is an important goal of the NIDA-funded Genes, Environment and Development Initiative (GEDI). In any genomewide association study (GWAS), the analysis of a large number of markers reduces the power to detect an effect from any individual marker when a given family-wise error rate is maintained. We therefore wish to identify markers with a heightened prior probability of showing an effect in G × E association analysis. We have identified three systematic approaches for choosing such markers: (1) Test for marginal additive effect: We expect that most markers that interact with environmental variation also will show at least a small marginal effect on the trait, but that effect might not be statistically significant. (2) MZ twin difference: We identify markers where genotype predicts the absolute phenotypic difference for pairs of MZ twins. A larger phenotypic difference between the two twins implies a larger difference in some unidentified environmental variation between the twins, and a genetic predictor of that difference implies genetic control of sensitivity to the environment. (3) Levene variance test: We identify loci where genotype is correlated with trait variance rather than trait mean. If a genotype is associated with increased variance, that implies genetic sensitivity (possibly of a nearby locus) to environmental influence or genetic influence of other genetic loci. A collection of N GWAS markers can be divided into two sets based on these screening tests with N1 markers in the theoretically enriched set and N2 remaining markers where N1 + N2 = N. To obtain a family-wise alpha-level of .05, we use two p-value cutoffs requiring $p <$ p1/N1 for the enriched set and $p <$ p2/N2 for the remaining markers where p1 + p2 = .05. Analyses of these approaches based on mathematical logic, computer simulation, and data from the GEDI project are discussed.

Genetic influences on life-span and its relationship to personality: A 16 year follow-up study of a sample of ageing twins

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Margaret Wright; Queensland Institute of Medical Research
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The idea of predicting health-behavior and mortality based on personality traits is of high interest to the public health system, especially

in light of the significant increase in life expectancy but also the age-related decline in various cognitive and physical domains. To date, the relationship between personality and life-span is not well understood and no study has examined genetic influences on this relationship. The present study aimed to explore the phenotypic and genetic relationship between personality and life-span as well as genetic influences on all-cause mortality. The prospective community-based study includes 3752 twin individuals over 50 years of age who completed a questionnaire assessing Neuroticism, Psychoticism, Extraversion, Social Desirability and Pessimism/Optimism at baseline using the Revised Eysenck Personality Questionnaire and the Revised Life Orientation Test, respectively. Information on age at death was obtained 16 years after initial assessment of personality. Extraversion was inversely related to mortality with the risk of death decreasing 3% per unit increase of the extraversion score. Psychoticism and pessimism were positively related to mortality with a 36 and 39% increase in risk of death per unit increase in the respective personality score. Neuroticism and Social Desirability were unrelated to all-cause mortality. Heritability of life-span was 7%. Cross-twin cross-trait hazard ratios were only significant for optimism/pessimism in MZ twins with no significant differences between MZ and DZ hazard ratios in all traits; however, there was a trend for slightly higher hazard ratios in MZ compared to DZ twins in psychoticism and optimism/pessimism. Extraversion, psychoticism and optimism/pessimism are significant predictors of longevity; extraversion is associated with a reduction and pessimism and psychoticism with an increase in mortality risk. Genetic influences on longevity in Australian twins are very low (7%). Our data also suggest a small, albeit non-significant, genetic influence on the relationship of pessimism and psychoticism with life-span.

The Gene, Environment, and Neighborhood Initiative (GENI) to understand a cluster of health outcomes in African American youth

Brian Mustanski; Northwestern University

Symposium: Gene-Environment Interaction in Substance Use and Externalizing Behavior: Genetic Research to Minority Populations and Rethinking Models.

African American (AA) urban adolescents are one of the groups at greatest risk of exposure to HIV, and impoverished urban youth show high rates of other problem behaviors, including drug use, alcohol abuse, and disruptive behavior disorders. AA youth have not been widely represented in studies of gene-environment interplay. The GENI study was guided by a framework that integrated neighborhood, family, and genetic factors as predictors of these multiple related outcomes. GENI took advantage of a natural experiment in which federal housing funds were used to relocate a quasi-random sample of AA families living in a severely impoverished public housing community to more advantaged lower-middle class neighborhoods. The families that participated in the study had been part of an ongoing longitudinal study, the Mobile Youth Survey (MYS), which provides multiple waves of existing pre-relocation data. The quasi-random assignment of families to neighborhood and existing pre-relocation data allows us to strongly test for gene-environment interaction effects on these outcomes. Data collection for GENI will be completed by the summer of 2011, and will include DNA and phenotypic data from 600 adolescents and their primary caregivers. Local crime statistics and national census data will be used to provide objective measures of key neighborhood characteristics associated with high risk behavior. The long-term goal is to use these data to develop biological, behavioral, structural, or multilevel interventions for urban, impoverished adolescents engaging in multiple problem behaviors—HIV risk taking, substance use, and disruptive behavior disorders. During this talk we will describe the study design with a particular focus on the formative and ongoing work to engage community members and leaders in the design of the study in a manner consistent with the bioethics concept of "community consent."

Cultural sensitivity in research: Specific considerations in conducting genetic research with African American populations

Aashir Nasim; Virginia Commonwealth University

Submitted as part of symposium: Gene-Environment Interaction in Substance Use and Externalizing Behavior: Taking Genetic Research to Minority Populations and Rethinking Our Models.

Public belief in the potential for genetic variation research (GVR) to contribute to improved health remains relatively strong, but research consistently shows lower acceptance of and willingness to participate in GVR by ethnic minority groups, especially African Americans. While the fear of information misuse is an oft-cited reason for non-participation across most U.S. populations, issues surrounding cultural and racial mistrust and stigma appear to be unique to the African American experience. Perhaps most disconcerting is that general wariness and mistrust of medical researchers by African Americans is not assuaged by education about genetic research and previous participation in GVR. This presentation will delineate reasons why African Americans may remain distrustful of GVR and also explore ways in which researchers might improve their relationships with African American study populations. Specifically, the framework for a culturally-sensitive approach to GVR is outlined based on culturally-congruent research methods, culturally-sensitive data interpretations, and culturally-informed theory and practice. The utilization of a culturally-sensitive approach may prove beneficial to efforts to increase the recruitment and retention of African Americans in GVR as well as help to improve future research participation.

Comparison of the power of the classical twin and extended pedigree designs to detect heritable variation

Michael Neale; Virginia Commonwealth University
Elizabeth Prom-Wormley; Virginia Commonwealth University
Lindon Eaves; VIPBG, Virginia Commonwealth University
Carol Franz; University of California San Diego
William Kremen; UC San Diego

Most initial forays into establishing the heritability of a trait use the classical twin study of MZ and DZ twin pairs who are reared in the same home. Although a study of separated MZ twins would provide greater statistical power to detect heritable variation, this design is not widely used because of the scarcity of such individuals, and possible non-representativeness of adoptees and their parents. The classical twin study seems a natural choice, as twins are common in the population and data analysis is straightforward. However, it has been suggested (e.g., Glahn DC, et al. (2010) Proceedings of the National Academy of Sciences U S A 107:1223–1228) that extended pedigrees (without twins) provide superior statistical power to detect heritable variation and better resolution between additive genetic and shared environmental factors. We directly compare the statistical power of

the two designs and show that, under most circumstances, the twin study provides substantially greater power per individual than does the study of extended pedigrees.

Analytic issues in next generation sequencing: Lessons from exome-wide sequencing of autism

Benjamin Neale; Massachusetts General Hospital

Next Generation Sequencing holds great promise for the analysis and interpretation of behavioral phenotypes. For the first time, we are capable of assaying nearly all of the variation in the human exome or genome. Such a wealth of data will undoubtedly improve our ability to gain new insights into the genetic architecture and biological basis of human phenotypic variation. However, how best to apply quality control, analytic methods and biological interpretation of this variation is still very much under development. In this work, I will describe the preliminary quality control and analysis of the NIMH ARRA Autism sequencing project. In this study, we conducted exome sequencing of approximately 1,000 samples with a mixture of case control and trio-based sequencing. I will describe the sample, target, and variant level QC of these data as well as initial bulk properties of the data.

The genetic and environmental etiology of internalizing and externalizing behavior in adolescent twins

Laura Baker; University of Southern California
Sharon Niv; University of Southern California
Adrian Raine
Catherine Tuvblad; USC

Comorbidity between internalizing (anxious, depressive) and externalizing (aggressive, delinquent) behavior is a well-established and common clinical reality throughout the lifespan, but perhaps becomes more significance in adolescence, when individuals are awarded more freedom. However, the genetic and environmental etiology of this comorbidity has rarely been examined in a behavioral genetic setting, especially during the period of adolescence. Additionally, research suggests that while caregivers may be more reliable reporters of externalizing behavior in youth, youth themselves are more reliable reporters of internalizing symptoms, raising the question of how different raters affect data patterns. Using the parent report Child Behavior Checklist (CBCL) as well as the youth report version (Youth Self Report—YSR), this research uses a twin study design to examine the etiology of coexisting internalizing and externalizing symptoms in mid adolescence (age 14–16 years) using a common pathway model that examined all data concurrently. Female comorbidity was accounted for by genetic and shared environmental influences, and male comorbidity by shared environmental influences, exclusively. Genetic influences emerged for all but self-report male externalizing behavior. Every scale showed unique influences as well, some of which were correlated between same-rater scales (e.g. parent report internalizing and externalizing), suggesting that some of the influences on covariation are rater-specific. These results contribute to our understanding of the nature of comorbid psychological disorders during adolescence, and suggest the importance of shared environment to the development of both internalizing and externalizing behavior.

Meta-analysis of genome wide association studies on heart rate variability

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Vinicius Tragante do Ó; University Medical Center Utrecht
Eric Whitsel; University of North Carolina at Chapel Hill
Kathleen Kerr; School of Public Health, University of Washington
Brenda Penninx; VU University Medical Center Amsterdam
Albertine Oldehinkel; University Medical Center Groningen
Joshua Bis; University of Washington
Jan Jouke Hottenga; VU University Medical Center Amsterdam
Bram Dierckx; Erasmus Medical Center Rotterdam
Joop Lefrandt; University Medical Center Groningen
Jared Magnani; Boston Medical Center
Christian Gieger; Helmholtz Zentrum München
Harriette Riese; UMCG/RuG
Susan Heckbert; University of Washington
Harold Snieder; Unit of Genetic Epidem. & Bioinformatics
Eco de Geus; VU University Amsterdam

On behalf of the GWA-RSA consortium:

Heart rate variability (HRV), or respiratory sinus arrhythmia (RSA), is a strong predictor of myocardial infarction (MI) mortality in both MI patients and the general population and reflects the influence of the parasympathetic branch of the autonomic nervous system on the heart. Heritability estimates of HRV measures show a wide range from 13 to 74%. Neither a genome-wide linkage analyses in the Framingham Heart Study using 725 members from 230 families and a 10 cM map nor a genome-wide association analysis of 548 individuals genotyped with a low density array of 71,000 single nucleotide polymorphisms (SNPs) yielded any significant hits. Furthermore only a few candidate gene association analyses have been conducted to date with limited results. In order to identify genes for HRV we set up a consortium consisting of 12 cohorts including over 24,000 Caucasian individuals for whom genome wide data are available on $\sim$ 2,500,000 SNPs. Each cohort analyzes three HRV measures, the standard deviation of the normal-to-normal intervals (SDNN), the root mean square of successive differences (RMSSD), and high frequency (HF) power or peak valley RSA (pvRSA), upon availability in the total cohort as well as in sex-stratified samples. A meta-analysis will be performed to combine the results of the different cohorts. The consortium has 80% power to identify gene variants that explain 0.17% of the variance in HRV, corresponding to e.g. an increase of 1.2-2.6 ms in RMSSD per risk allele depending on the minor allele frequency.

Serotonin transporter gene and distress intolerance in binge drinkers living with HIV

Nicole R. Nugent; Alpert Brown Medical School
Michelle Lally; Alpert Brown Medical School
Larry Brown; Alpert Brown Medical School
Valerie Knopik; Alpert Brown Medical School
Susan Frater; Alpert Brown Medical School
John McGeary; Alpert Brown Medical School

Distress tolerance may mitigate the effects of distress on reduced engagement in health behaviors among persons living with HIV. A genetic variant of the serotonin transporter gene (5-HTTLPR) has been linked to distress tolerance and has been found to moderate the effects of stress on a range of mental health outcomes. Participants reporting recent binge drinking were recruited from HIV-clinic visits;

201 participants (55 female, 146 male) provided DNA and completed an assessment of four aspects of distress tolerance: tolerance, appraisal, absorption, and regulation. Triallelic 5-HTTLPR genotypes were coded for the presence of a less transcriptionally-efficient allele (i.e., s'). After adjusting for age, race, gender, education, and self-reported CD4+ count, participants with s' allele reported greater levels of absorption and tolerance but did not evidence differences in appraisal or regulation. Absorption and tolerance appear to be uniquely associated with the less-transcriptionally efficient alleles in binge drinkers living with HIV.

OPRM1 and diagnosis-related posttraumatic stress disorder in binge-drinking patients living with HIV

Nicole Nugent; Alpert Brown Medical School
Michelle Lally
Valerie Knopik; Brown University
Larry Brown
John McGeary; Providence VAMC/Brown University

Posttraumatic stress disorder (PTSD) has been linked to numerous negative outcomes in persons living with HIV (PLH) and there is evidence that PTSD symptoms may play a role in maintaining alcohol use problems. The opioid receptor mu-1 (OPRM1) may play an important but different role in both PTSD and alcohol use. We examined the association between PTSD and drinking motives as well as OPRM1 as a predictor of both PTSD and drinking motives in a sample of 201 PLH reporting recent binge drinking. Self-reported PTSD symptom severity was significantly associated with drinking motives for coping, enhancement, and socialization. OPRM1 was associated with PTSD symptom severity as well as enhancement motives for drinking.

Dopamine and vasopressin moderate the Influence of mother and father warmth on externalizing and competence behaviors across childhood and adolescence

Caitlin O'Brien; Arizona State University
Kathryn Lemery-Chalfant; Arizona State University
Hill Goldsmith; University of Wisconsin

Externalizing behaviors are disruptive across multiple settings and predict later antisocial outcomes (T.E. Moffit, 1993, Development & Psychopathology, 131, 533–554). The longer allele of the dopamine receptor DRD4 is associated with higher novelty seeking (L.A. Schmidt et al., 2001, Psychiatric Genetics, 11, 25–29), which underlies externalizing by increasing impulsiveness and stimulation-seeking (S. Barnow et al., 2005, Aggressive Behavior, 21, 24–39). Vasopressin, a neuropeptide related to dopamine release, predicts animal aggression (I.W. Craig & K.E. Halton, 2010, Encyclopedia of Life Sciences). Less positive parenting also relates to externalizing problems (K. Deater-Deckard et al., 1998, Development and Psychopathology, 10, 469–493). Parenting and behavior were measured on continuums (parental rejection-warmth and externalizing-competence behavior) to test the differential susceptibility hypothesis (internal characteristics increase vulnerability to both positive and negative environmental effects). Dopamine and vasopressin (AVPR1a) in conjunction with warmth/rejection were examined longitudinally in a sample of predominantly Caucasian (92%) twins from childhood (T1; mean age 7.4) to adolescence (T2; mean age 14.0). Longer variants on both genes were hypothesized to be plasticity alleles. Externalizing/competence fit an AE model across mother (MR) and father report (FR) of externalizing/competence (MR T1 a2 = .73, T2 a2 = .67). Heritability of T1 MR and T2 FR externalizing/competence was moderated by warmth/rejection such that externalizing/competence was less heritable under conditions of lower warmth. Despite significant concurrent interactions, longitudinally DRD4 did not interact with T1 warmth/rejection to predict change in externalizing/competence at T2. For AVPR1a, adolescents with two long alleles had marginally higher externalizing when exposed to childhood rejection and higher competence when exposed to childhood warmth than those with a short allele [B(256.88) = 0.08, SE = 0.05, $p = 0.07$], controlling for T1 externalizing/competence. Warmth/rejection is a salient environmental influence that moderates the heritability of child/adolescent behavior. Although dopamine is more frequently examined, vasopressin may have a unique influence on the development of externalizing/competence.

Chromogranin A (CHGA) and the autonomic system in twin pairs

Daniel O'Connor; UCSD

Chromogranin A is a determinant of catecholamine storage vesicle formation, and its catecholamine release inhibitory fragment catestatin inhibits release at the nicotinic cholinergic receptor. Genetic diversity at the CHGA locus predicts not only CHGA secretion but also autonomic function and BP. CHGA fragments display substantial heritability in twin pairs. We have undertaken genome wide linkage and association to position loci influencing CHGA release and autonomic function.

Heritability of a simple preventive behavior. getting the Flu vaccine

Juan Ordonana; University of Murcia
Juan Sanchez-Romera; University of Murcia
Lucia Colodro; University of Murcia
Francisco Perez-Riquelme; Murcia Health Council
Irene Rebollo-Mesa; King's College London

Introduction: Getting a vaccine is a simple preventive behavior with important implications for health promotion. Compliance with disease detection and prevention programs is influenced by health policies and by social and individual factors. Every year, during the last trimester, health promotion campaigns try to promote flu vaccination among the elderly and other risk groups. Our objective was to estimate genetic and environmental effects on individual differences in this preventive behavior.
Methods: The data comprised adult female twins from the Murcia Twin Register (Spain) (191 MZ and 190 DZ pairs). Mean age = 53.1 (Range = 43–70). Preventive behavior was based on self-report. Zygosity was ascertained by questionnaire. A threshold model for categorical data was fitted to quantify genetic and environmental influences on variation in vaccination behavior.
Results: Only 22.3% of the sample had got a flu vaccine. Tetrachoric correlations were higher for MZ twins [MZ: 0.754 (IC 95%: 0.584, 0.870); DZ: 0.384 (IC 95%: 0.146, 0.587)]. Model fitting suggested that an AE model offered the best fit to the data with a heritability estimate of .76 (IC 95%: 0.605, 0.871).

Conclusion: Preliminary results suggest that genetic differences may affect the probability of practising a relative simple and voluntary preventive behavior. However, we did not find any detectable effect of shared-environment on this variable.

Sleep quality in adult women: Genetic and environmental effects

Juan Ordonana; University of Murcia
Irene Rebollo-Mesa; King's College London
Francisco Perez-Riquelme; Murcia Health Council
Bruno Ribeiro-do-Couto; University of Murcia
Jose Martinez-Selva; University of Murcia

Introduction: The Pittsburgh Sleep Quality Index (PSQI) is a widely used measure which assesses different components of sleep quality. Recently, a relevant genetic effect on sleep quality has been reported for young people using this index (Barclay et al., 2010, Chronobiol Int, 27, 278296). Our objective was to investigate the genetic and environmental influences on variation in sleep quality in a sample of adult women.
Method: The data comprised adult female twins from the Murcia Twin Register (Spain) (209 MZ and 222 DZ pairs) in Spain. Mean age = 53.1 (SD: 7.5; Range = 43–70). The PSQI questionnaire was administered during a personal interview. Using algorithms, items are combined to form 7 scales (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction). These components can be summed to yield a global score ranging from 0 to 21 (Higher scores mean worse sleep quality). Additionally, the global score can be dichotomized into two levels ("Good" or "poor sleep quality").
Results: Preliminary data show that mean score for global sleep quality was 5.84 (SD: 4.1; Range: 0–19). About a third (33.8%) of the total sample scored 6 or higher which is associated with poor sleep quality. Correlations for the PSQI index were .44 and .18 for MZ and DZ twins respectively. Model fitting suggested that an AE model offer the best fit (A: .44; E: .56). A threshold models for categorical data fitted to the dichotomized data showed also a relevant genetic effect (A: .53; E: .47).
Conclusion: Our analysis confirms the importance of genetic and non-shared environmental influences on these variables in a sample of adult women. Family-wide influences do not seem to help explaining variance in sleep quality.

Possible sex differences in genetic and environmental influences on measures of socioeconomic status—results from a Norwegian study of young adult twins

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Nikolai Czajkowski
Gun Peggy Knudsen; Norwegian Institute of Public Health
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Kristian Tambs; Norwegian Institute of Public Health
Ted Reichborn-Kjennerud; Norwegian Institute of Public Health

Socioeconomic status, measured as e.g. educational attainment, occupation or income is important both as primary endpoint and as a moderator in behavioural genetic research. Familial transmission of socioeconomic status is influenced by both genetic and shared environmental factors, but the relative importance of these factors differs across time and cultures. In today's Norway, admission to higher education is free and primarily based on academic achievement. Although more women than men have university degrees, women still choose traditional female occupations, and earn considerably less than men. The reasons for this discrepancy are traditionally attributed to social influences, as little is known about sex differences in genetic and environmental contributions to measures of socioeconomic status.

With data from The Norwegian Twin Registry, we are currently conducting a registry linkage study including data on educational attainment, income, occupational status as well as work disability and sickness leave. The 7,710 twins (3,111 complete pairs) included in the study were born between 1967 and 1979, and have previously answered a comprehensive questionnaire on somatic and mental health. A subset of 2 801 twins have also participated in two psychiatric interviews covering Axis I and Axis II disorders.

At the conference, we will present preliminary uni- and multivariate analyses on genetic and environmental contributions to various measures of socioeconomic status, with special emphasis on possible sex differences in genetic and environmental contributions to educational attainment, occupational status and income level.

Identifying the univariate ACDE model

Koken Ozaki; The Institute of Statistical Mathematics

One of the biggest problems in classical twin studies is that it cannot estimate additive genetic (A), non-additive genetic (D), shared environmental (C), and non-shared environmental (E) effects, simultaneously, because the model, referred to as the ACDE model, has negative degrees of freedom when using Structural Equation Modeling (SEM). Therefore, instead of the ACDE model, the ACE model or the ADE model is actually used. However, using the ACE or ADE models almost always leads to biased estimates. In this talk, some techniques (including non-normal structural equation modeling) to identify the univariate ACDE model will be discussed.

Common genetic influences on vulnerability to drug dependence from adolescence to young adulthood

Rohan Palmer; Division of Behavioral Genetics
Tanya Button; University of Colorado
Robin Corley; University of Colorado
Christian Hopfer; University of Colorado at Denver
Michael Stallings; University of Colorado
John Hewitt; University of Colorado

Background: During adolescence and young adulthood there is a general tendency to use and abuse multiple substances. This study investigated which etiological factors contribute to the latent risk for multiple drug problems across adolescence and young adulthood.
Methods: Data were drawn from a longitudinal sample of 2745 adolescents followed from adolescence into young adulthood. Lifetime Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) alcohol, tobacco, and cannabis dependence symptom counts were assessed during adolescence and past year dependence symptom counts were assessed during young adulthood. Biometrical models were used to estimate the magnitude of genetic and environmental influences on the liability to endorse dependence symptoms on multiple substances over time.
Results: The relationship between the latent risk for drug dependence during adolescence and young adulthood was primarily attributable to

a genetic factor common to adolescence and young adulthood. Sex differences in the magnitude of genetic and environmental influences on each substance were due to substance-specific mechanisms.
Conclusions: Results from our genetic analyses suggest that alcohol, tobacco, and cannabis dependence are heritable disorders and that the stability of the latent risk for drug dependence is primarily driven by persistent genetic effects.

Systems genetics of addiction: A conceptual approach using alcohol dependence as an example

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Sarah Francazio; Providence College, Providence, Rhode Island
John McGeary; Providence Veterans Affairs Medical Center, Division of Behavioral Genetics, Rhode Island Hospital, Department of Psychiatry and Human Behavior at Brown University
Valerie Knopik; Division of Behavioral Genetics, Rhode Island Hospital, Department of Psychiatry and Human Behavior at Brown University

Despite the availability of whole-genome data and bioinformatics databases, small portions of the variability in addiction phenotypes are explained by measured genetic differences considered individually. Approaches that transcend parametric statistics that need adjustments to limit type 1 errors would enhance this line of research. Traditional association methods are limited because complex epistatic and environmental assumptions hold true, as evidenced by complex biological systems. We will discuss what can be gained from using computational approaches and systems biology over traditional genetic association. These newer association approaches rely on prior knowledge of candidate genes and biological mechanisms allowing them to characterize the joint distribution of genetic effects and biological mechanisms within a given dataset. We will use alcohol dependence as an example phenotype because it is largely heritable and we have some understanding of its neuronal and pharmacological mechanisms.

Genetics of the associations between adolescent indicators of behavioral disinhibition and young adult measures of alcohol, tobacco and other substance use disorders

Rohan Palmer; Division of Behavioral Genetics
Susan Young, IBG
Michael Stallings; University of Colorado
Robin Corley; University of Colorado
Christian Hopfer; University of Colorado at Denver
Valerie Knopik; Brown University
John Hewitt; University of Colorado

Background: Indicators of Behavioral Disinhibition (BD) affect the likelihood of developing substance related problems. While each of these phenotypes are heritable, it remains unclear how early ADHD, conduct disorder (CD), and novelty seeking tendencies (NS) relate to adult indicators of the liability to abuse multiple substances. Further, it is unclear how much of that relationship is explained by shared genetic and environmental mechanisms? This study investigated which genes and environment contribute to the covariance between childhood/adolescent indicators of BD and the liability for substance use disorders.
Methods: 767 individuals from the Colorado Twin Study, who participated at the adolescent and young adult waves of assessment, were assessed for lifetime DSM-IV ADHD Hyperactivity-Impulsivity and Inattention symptoms, CD, and NS during adolescence, and lifetime alcohol, tobacco, cannabis, amphetamine, cocaine, hallucinogen, inhalant, phencyclidine, opiate and sedative substance use disorder symptoms during young adulthood (conditional on exposure). Exploratory factor analysis was used to identify and extract factors using ADHD, CD, NS in adolescence, and SUDs in young adulthood. Phenotypic associations between factors were determined after adjusting for age effects and family structure. A trivariate Cholesky was used to partition the variance and covariance between the factors.
Results: Factor analyses indicated a Substance Addiction Vulnerability (SAV) factor comprised of all substances, an externalizing factor comprised of CD and NS, and an ADHD factor comprised of inattention and hyperactivity/impulsivity. There was no evidence of qualitative sex differences and parameters could be constrained across genders for all measures. All phenotypes were significantly heritable (>30%) with limited shared environmental effects. Genes account for the majority of the comorbidity among ADHD, EXT, and SAV (rg ranges from 0.43 to 0.56).
Conclusion: Pleiotropic genes explain the comorbidity between ADHD, EXT, and SAV; these effects are not entirely common to all three constructs.

Effects of cortisol and testosterone on the genetic and environmental determinants of hippocampal volume

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Hong Xian; Washington University School of Medicine
Anders Dale; University of California San Diego
Lindon Eaves; VIPBG, Virginia Commonwealth University
Christine Fennema-Notestine
Carol Franz; University of California San Diego
Michael Grant; Boston University
Richard Hauger; University of California San Diego
Kristen Jacobson; The University of Chicago
Michael Lyons; Boston University
Sally Mendoza, University of California Davis
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Cortisol and testosterone have both been shown to be associated with brain structure and function in middle-aged and older adults. Despite similar sites of action within the brain, as well as evidence of antagonistic effects on one another, the simultaneous effects of these hormones on brain structure have yet to be examined. In previous findings from the Vietnam Era Twin Study of Aging (VETSA) we demonstrated that testosterone moderates the genetic and environmental determinants of hippocampal volume. In the present study we extend this work to include the effects of cortisol, as well as the interaction of cortisol and testosterone, in order to investigate the extent to which multiple neuroendocrine factors influence the genetic and environmental determinants of hippocampal volume. Participants were 91 MZ twin pairs, 83 DZ twin pairs, and 34 unpaired twins ages 51–59. The moderating effects of average daily levels of cortisol, testosterone, and their interaction on the means and variance components of hippocampal volume were simultaneously examined using linear moderator models in Mx. Independently, both hormones were found to influence the genetic determinants of hippocampal volume,

while no effect was seen on the means. When both hormones and their interaction were included in the model, significant mean effects on hippocampal volume were observed. After accounting for these mean effects, the genetic variance for hippocampal volume was found to be primarily influenced by the testosterone level, while the environmental variance was primarily influenced by the interaction between the hormones. These findings suggest that the genetic and environmental determinants of hippocampal volume are sensitive to the effects of multiple neuroendocrine factors. Moreover, they highlight the need to simultaneously examine the effects of different neuroendocrine factors, rather than study individual hormones in isolation.

Association of COMT with continuous performance task indices

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Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable child psychiatric disorder, leading researchers to search for specific genes contributing to its etiology. Molecular genetic studies attempting to identify susceptibility genes for ADHD have yielded largely inconsistent findings. Instead of focusing on manifest diagnoses or symptom dimensions, using endophenotypes may produce stronger, more replicable results. Neurocognitive deficits have been proposed as potentially valid and useful endophenotypes for ADHD. The Continuous Performance Task (CPT) is a widely used neurocognitive measure of sustained attention and impulsivity. There are inconsistent findings regarding the CPT's relation with ADHD, which could be due to variations in the CPT parameters indexed across studies. Sensitivity, bias, and performance variability are CPT indices that have shown consistently strong relations with ADHD symptoms, relative to more traditional CPT indices (e.g., omission and commission errors). These CPT indices have been shown to be underlied by prefrontal regions of the brain, a critical region in aspects of attention. In this study, we examined d', a measure of sensitivity, and $\ln\beta$, a measure of response bias, which are CPT indices derived from Signal Detection Theory. A link between the prefrontal cortex (PFC) and target-detection sensitivity (d') has been found, as well as between the PFC and response bias. Increased variability in performance has also been associated with the PFC, and examining variability in errors over time may provide more robust findings by capturing dynamic trial-by-trial changes, relative to overall scores. In the present study we tested the association of these CPT indices with a candidate gene that is highly expressed in the PFC (i.e., COMT) in a sample of 500 clinically-referred and non-referred children who ranged in age from 6 to 16. Findings from this study should illuminate the genetic etiology of ADHD and its component neurocognitive traits.

On the association of common and rare variation influencing body mass index: A combined single nucleotide polymorphism and copy number variation analysis

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Genetic factors have consistently been demonstrated to influence individual differences in body mass index (BMI), with heritability estimates in the order 0.70. Genome-wide association studies of BMI using large samples ($n > 30{,}000$) have yielded robustly associated variants of individually small effect. It is likely that structural variants other than common single nucleotide polymorphisms (SNPs) affect body composition. A growing list of common and rare copy number variants (CNVs) have been associated with moderate and extreme obesity. The purpose of this research was to perform a combined analysis of common and rare genetic variation associated with BMI in 735 European-Americans from the Collaborative Study on the Genetics of Alcoholism (COGA). Given small effect sizes of BMI associated variants the power to detect genome-wide significant associations in COGA is limited. Therefore, we employed a sum score approach, since aggregate risk should be significant if a sufficient proportion of variants have real effects. A sum score of 56 top-ranking SNPs catalogued from BMI meta-analyses was significantly associated ($p < 0.01$) with BMI accounting for 0.8% of the variance. A total of 79 obesity-associated CNV regions were identified from the literature, of which 25 were found in COGA with suggestive evidence of replication of a common duplication on 15q11.2 accounting for 0.5% variance in BMI. Rare CNV burden score incorporating duplications with prior association with obesity was significantly associated with BMI accounting for 0.7% of the variance. A model including standard covariates, SNP sum score, common duplication on 15q11.2 and rare CNV burden score accounted for 7.3% of the variance in BMI($F(11,722) = 5.168$, $p = 2.5 \times 10^{-8}$). Area under receiver operator criteria curve (AUC) estimates indicated that the model significantly predicted obesity classification (AUC = 0.625, 95% CI = [0.577, 0.672], $p = 8.1 \times 10^{-7}$). As association analyses of complex traits incorporate a widening spectrum of genomic variation, there is a need for improved analytical approaches to best integrate the respective contributions of common and rare polymorphisms.

The genetic structure of personality is complex, not simple: Evidence and implications

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In search of the biological origins of the Five-Factor Model (FFM), researchers have studied the structure of genetic covariance matrices, that is, the genetic cross-correlations among items in twin pairs. Such studies have repeatedly found that the FFM exists at the genetic level, and concluded that the FFM is in some shape or form biologically based. However, the degree to which the factor solutions conform to simple structure is rarely examined. If the genetic matrices have complex rather than simple structure, it would suggest that the FFM is but one out of many possible interpretations of the multidimensional space, and that there is nothing special about the FFM traits per se from a biological perspective. We examined the degree of simple structure in genetic covariance matrices based on the California Psychological Inventory (CPI) and the Adjective Checklist (ACL) among a sample of 839 identical and fraternal twins. The multivariate complexity of the genetic covariance matrices based on the CPI and ACL was compared to simulated factorial solutions with increasing degrees of simple structure. Results revealed a high degree of complexity in the genetic structure of both inventories, regardless of whether factors were extracted using a scree plot or parallel analysis, or whether items or scales were analyzed. Thus, although rotated

genetic factors may resemble phenotypic factors, personality items do not cluster in particular areas of space, either at the genetic or phenotypic level; rather, they are uniformly distributed, weakening the argument for rotation to a particular mapping system such as the FFM. We conclude that no particular mapping system is more endogenous or biologically based than any other, and that it may be multidimensional personality structure in general, rather than a given rotational configuration, that is heritable or otherwise based in biology.

Using project talent twin data to estimate the range of the components of variance of high-order cognition

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Project Talent (PT) was a large, nationally representative longitudinal study of men and women conducted by the American Institutes for Research. In 1960, $N \sim 440{,}000$ high school students completed a four-day battery of measures designed to provide baseline data on aptitudes, abilities, interests and aspirations (Flanagan et al. 1962; www.projecttalent.org). Ability measures included cognition, language, mathematics, and reasoning. Several higher order factors of cognition, including fluid (Gf) and crystallized (Gc) intelligence can be extracted from these data (McArdle 2010). The expected number of twin pairs in a population of >400,000 is ~4000 pairs, even adjusting for differential mortality of twins. Thus, the PT data forms one of the largest U.S. twin studies of cognition and abilities. Because zygosity of same-sex pairs is generally unknown (except for ~500 pairs), we explored several alternatives to assigning classifications. One is a sensitivity approach to estimation (as in Prescott et al., 2007) by which the prevalences of opposite sex pairs and the male:female ratio in the sample overall are used to place bounds on the Ns of male and female DZ pairs, with the remaining pairs assumed to be MZ. Data on pair similarity for height and weight were used to create several classifications and the impact of these on heritability estimates of cognition examined.

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Genetic and environmental contributions to the relationships between brain structure and cigarette use

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Chronic cigarette use has been associated with large-scale differences in the neuroanatomy of smokers relative to nonsmokers in case–control studies. However, the etiology of the relationships between brain structure and cigarette use is unclear. A community-based sample of male twin pairs ages 51–59 (110 monozygotic pairs, 92 dizygotic pairs) was used to determine genetic and environmental overlap between brain structure and cigarette use.

Brain structure was measured by high-resolution structural magnetic resonance imaging, from which subcortical volumes, and cortical volumes thicknesses and surface areas were derived. Bivariate genetic models were fitted between these measures and cigarette use measured as pack-years.

Positive phenotypic correlations were detected between cigarette use and lateral ventricle measures as well as white matter abnormalities, which were attributable to genetic effects. Widespread negative phenotypic correlations were detected between cigarette use and several cortical regions, including some frontal lobe regions; these correlations were attributed to either genetic or environmental influences.

A behavioral genetic investigation of the role of impulsivity in adolescent alcohol use

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Impulsivity and sensation seeking have long been associated with increased alcohol use during adolescence. Although this association has primarily been interpreted as representing the influence of personality on alcohol use, extant data are also consistent with several other propositions. Some evidence suggests that transactional relations may underlie their longitudinal association: Just as impulsivity and sensation seeking may influence alcohol use, greater alcohol use may reciprocally exacerbate maladaptive patterns of personality development. In addition, alcohol use and personality may be associated because they share common genetic influences. The current study used longitudinal, behavioral genetic data on 2,292 adolescent sibling pairs from the National Longitudinal Study of Youth who were assessed biennially from age 15 to age 19. In cross-lagged panel analyses, we found significant bidirectional associations, such that initial levels of impulsivity and sensation seeking predicted future alcohol use, while initial levels of alcohol use predicted future changes in impulsivity. Moreover, behavioral genetic analyses indicated that the longitudinal association between impulsivity and increases in alcohol use could not be entirely attributed to common genetic predispositions; rather, impulsivity had environmentally mediated effects on later alcohol use. In contrast, the present analyses could not discriminate among environmental and genetic influences on the association between alcohol use and subsequent change in impulsivity.

Does accounting for antihypertensive medication alter the heritability of blood pressure?

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Hypertension is a common disease that is implicated as a risk factor for impaired cognition, mood, and age-related brain abnormalities. A previous family study with a wide age range suggested that heritability estimates of blood pressure (BP) are confounded by the effects of antihypertensive treatment. Identifying a model to correct for BP-lowering medications is important for applications in twin analysis of BP and its relationship to other phenotypes.

We assessed BP and antihypertensive medication status in 1237 male twins (age 51–60 years) from wave 1 of the Vietnam Era Twin Study of Aging (VETSA). We used three approaches to adjust BP measurements for antihypertensive treatment. These approaches include: addition of a fixed value of 10 mmHg and 5 mmHg to measured systolic and diastolic BP, respectively, for subjects on any antihypertensive medication; incremented addition of mmHg to BP based on the number of medications used; and addition of mmHg according to the antihypertensive drug class. We used the classical twin design to compute the heritability of the corrected BPs and related measurements (e.g. ankle-arm index, mean arterial pressure estimates, pulse pressure) for each approach. We also assessed the relationship between BP traits and other traits measured in VETSA.

Adjusting for antihypertensive treatment did not significantly affect the heritability of BP measurements in the VETSA cohort. However, we did find that addition of mmHg for antihypertensive treatment resulted in higher correlations between BP and other traits (e.g. body mass index).

Our data suggest that not correcting for antihypertensive medication may not greatly impact the results of twin analysis when investigating BP in a cohort of middle-aged men. However, adjusting for antihypertensive medication may provide more power to detect relationships between BP and other traits, and it may have different effects on heritability as participants get older.

The role of early cognitive ability and positive parenting on antisocial behavior

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Parenting may be a significant mediator of the association between low cognitive ability and higher antisocial behavior. Cognitive deficits may evoke negative parenting, which may in turn lead to higher antisocial behavior. Evidence demonstrating that parenting mediates the association between cognitive ability and antisocial behavior would be consistent with this hypothesis (although it would not provide conclusive evidence). Parenting and family environment also may moderate the association between cognitive ability and antisocial behavior. A favorable social learning environment may decrease the impact of low cognitive ability, or children with lower cognitive ability may be particularly reactive to negative parenting.

The present study examined cognitive ability measured during toddlerhood and parents' cognitive ability as a predictor of antisocial behavior assessed during childhood and adolescence, examining positive parenting as a potential mediator and moderator. The sample included 970 individuals from two longitudinal twin studies. Positive parenting was assessed in via observers' codes of interactions between mothers and infants at ages 7, 9, 14, 24, and 36 months. Assessments of cognitive ability included measures of general intelligence, receptive and expressive language skills, and word comprehension at ages 14, 20, 24, and 36 months. Antisocial behavior was assessed in 922 children via parent report at age 4, 5, 7, 9, 10, 11, and 12 years, via teacher report at age 7, 8, 9, 10, 11, and 12 years, and via self report at age 17. Higher cognitive ability during toddlerhood, and higher parents' cognitive ability, and more positive parenting were associated with lower antisocial behavior during childhood and adolescence. However, there was no significant evidence suggesting that positive parenting is a mediator or moderator of the association between cognitive ability and antisocial behavior.

Social mechanisms in gene-environment interaction: Findings from the early growth and development adoption study

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A growing body of research has demonstrated interactions between individuals' genotypes and favorable or unfavorable environments in predicting psychological adjustment. Multiple theories have been proposed to explain the mechanisms whereby environments may offset or exacerbate genetic influences. We examine four mechanisms empirically defined by four different interaction patterns: (1) the stress-sensitivity mechanism, in which genetic vulnerability influences adjustment only in unfavorable environments 1; (2) the differential susceptibility mechanism, where individuals with particular genotypes are both more vulnerable to environmental stressors and also benefit from favorable environments 2; (3) the opportunity-knocks mechanism, where inherited characteristics have a greater impact in favorable environments; and (4) the specific nutrient mechanism where individuals with a high-risk genotype benefit from an enriched environment while those with a low risk genotype evidence more problems. In this presentation, results from the first 361 families enrolled in the Early Growth and Development Study, an on-going prospective full adoption design of yoked target children, adoptive parents, and birth parent(s), will be summarized to illustrate patterns of gene-environment interaction on social behavior during infancy and toddlerhood. The current paper examines the nature of the interaction effects by phenotype, focusing on patterns identified across studies. To date, we have found interaction patterns supporting the differential susceptibility mechanism, the opportunity-knocks mechanism, and the specific nutrient mechanism. Discussion will focus on how the cumulative results have potential to increase knowledge about specificity of mechanisms of G $\times$ E interaction, in connection with other work in the field.

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Do the same or different genetic factors predict pre- versus post-anxiety to 35% CO_2 enriched air?

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Persons with panic disorder (PD) or PD with agoraphobia are known to be hypersensitive to carbon dioxide (CO_2) enriched air, often experiencing a panic attack or reacting anxiously when breathing CO_2 enriched air. This finding suggests that CO_2 hypersensitivity is a vulnerability marker for PD. Three-hundred-forty-six twin pairs from the general population-based Norwegian NIPH Mental Health Study were exposed to a 35% CO_2 air mixture. All twins completed an anxiety symptom measure before and after exposure to ambient air as well as a 35% CO_2 air mixture. Two hypotheses regarding genetic risk factors for CO_2 hypersensitivity were examined. One hypothesis predicts that a single set of genetic risk factors impacts anticipatory anxiety before exposure to 35% CO_2 and these same genes constitute the only genetic influences on anxiety in response to exposure to 35% CO_2. The second hypothesis predicts that there are genes unique to anxiety in response to CO_2 such that but these unique genes become active or "turned on" in response respiratory stimulation via 35% CO_2. Our results support the latter hypothesis, with an AE model being the best fitting. Model results indicated that an additional 20% of variance is explained by a unique set of genes after response to 35% CO_2. Implications of findings and their relevance to understanding the role of genetic and environmental factors in CO_2 hypersensitivity will be discussed.

Behavior problems and timing of menarche: A developmental longitudinal biometrical analysis using the NLSY-children data

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A powerful longitudinal data source, the National Longitudinal Survey of Youth Children data, allows construction of a longitudinal trajectory of behavior problems, which can be linked to timing of menarche. We construct behavior problem measures for childhood, early adolescence, and a delinquency measure in late adolescence. Timing of menarche is self-reported, usually within a year of when it actually occurred. In a preliminary analysis, we evaluate the bivariate relationships between each measure of conduct disorder and the timing of menarche. Correlations were consistently null. However, biometrical structure with interesting and interpretable pattern underlies these null relationships.

In the major part of our study, timing of menarche was used to moderate the developmental trajectory of behavior problems, within a genetically-informed design. Results diverged for girls who reached puberty early versus those who did not. Girls reaching menarche early had both univariate and time-related multivariate behavior problem variance accounted for by the shared environment. Those reaching menarche with average/late timing had univariate and time-related multivariate behavior problem differences accounted for by genetic variance. Our findings match previous empirical results in important ways, and substantially extend those results.

These results support previous theory and empirical work suggesting that there is are critical features of the early shared environment that relate to age at menarche. These findings do not evaluate either the direct causal link between early childhood and timing of menarche or to the selection interpretation of this finding. However, they do enhance the empirical status of the link between the early childhood and eventual timing of menarche, which has previously been shown to pass through father presence/absence, divorce, and childhood environmental stress. The current study shows that the link also passes through problem behaviors, and is stable (through shared variance) over a long period of time lasting from childhood until early adolescence.

A genome-wide association study of multiple autistic traits in 8- and 12-year-olds

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Autism spectrum disorders (ASD) are highly heritable neurodevelopmental conditions (Ronald, A. & Hoekstra, R.A. (in press) Neuropsych Genet). A high proportion of relatives of individuals with ASD show subthreshold autistic tendencies (known as the broader autism phenotype), and autistic traits in the general population show a similarly high heritability to diagnosed ASD (Ronald, A. et al. (2006) J Am Acad Child Adolesc Psychiatry 45: 691–699). These findings support the hypothesis that ASD may be at least partly caused by common genetic variants. Analyses were conducted on individual genotyping data of 4000 unrelated children in the Twins Early Development Study (TEDS), a UK-based community sample. The Affymetrix 6.0 microarray platform was employed. Parents reported on the twins' autistic traits at ages 8- and 12-years using the Childhood Autism Spectrum Test (CAST; Scott, F.J. et al. (2002) Autism 6: 9–31). The CAST includes a total scale and three subscales (social impairments, communication difficulties, and restricted repetitive behaviours and interests). Prior to the analyses, rigorous quality control procedures were conducted: low quality samples and low quality single nucleotide polymorphisms (SNPs) were rejected. Non-typed SNPs were imputed. Population stratification was controlled for by the inclusion of eight eigenvectors as covariates. Single SNP association analyses were conducted using the SNPTEST program. Cluster plots of SNPs showing associations with $p < 1-e5$ were inspected and linkage disequilibrium between SNPs was analysed. Fifteen uncorrelated SNPs with the most significant associations are

currently being followed up in an independent replication sample for association with autistic traits. This includes two SNPs with $p < 5-e7$ associations with the communications difficulties subscale at age 8- and age 12-years, respectively. These findings represent the first genome-wide association study of autistic traits using individual genotyping data. Findings are discussed in relation to future research designs to uncover variants associated with autistic traits and ASD.

Does difficult temperament moderate genetic and environmental influences on behavior problems?

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Belsky's (1997, Psych Inquiry, 8, 182–186) theory of differential susceptibility to environmental influences suggests that children with difficult temperaments may be more affected by the environment than children with easier temperaments. We tested this prediction by exploring difficult temperament as a moderator of genetic and environmental influences on externalizing problems in early childhood. Belsky's theory would predict that environmental contributions to behavior problems should be greater for children who score higher on measures of difficult temperament.

The temperament and problem behaviors of 144 monozygotic and 168 dizygotic 2-year-old twin pairs were assessed via parent-rating questionnaires. Two measures of difficult temperament were examined: (1) Negative emotionality. High scores on this measure reflects a child who displays high levels of anger, distress and fear (i.e., are more difficult). (2) Soothability. Children who score high on this measure are easily calmed and recover quickly from distress (i.e., are less difficult). Externalizing behavior problems were assessed with the Child Behavior Checklist.

Biometric moderator models (Purcell, 2002, Twin Res, 5, 554–571) were fit to the data. The results were similar whether difficult temperament was conceptualized as high negative emotionality or low soothability. The genetic and shared environmental interaction parameters were significant indicating that genetic and shared environmental effects differ across levels of difficult temperament. When children have difficult temperaments, genetic contributions to externalizing problems are highest and shared environmental influences lowest. In contrast, shared environmental contributions to behavior problems were highest and genetic influences lowest when children had easier temperaments.

These findings provide evidence of differential environmental susceptibility, however, contrary to Belsky's prediction; it is not the difficult children who are most susceptible to environmental influences. For children with easy temperaments variation in externalizing problems is largely due to shared environmental influences whereas such effects are negligible when children have difficult temperaments.

Association between autistic traits and internalising traits in early adolescence: A twin study

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Autism spectrum disorders (ASD) show a high degree of comorbidity, with an estimated 70% of individuals with ASD having an additional psychiatric disorder (Simonoff et al. 2008 J Am Acad Child Adolesc Psych 47: 921–929). Anxiety disorders in particular are among the most commonly co-occurring conditions with ASD. The current study aimed to explore the causes of the overlap between autistic traits and internalising traits in adolescence. This was assessed in 12- to 14-year-olds and participants came from the Twins Early Development Study (TEDS), a UK-based general population sample. Parents completed the emotional symptoms scale of the Strengths and Difficulties Questionnaire (SDQ, Goodman 1997 JCPP 38: 581–586) and the Autism Spectrum Quotient (AQ, Baron-Cohen et al. 2006 JADD 36: 343–350). The degree to which internalising traits and autistic traits are caused by the same genetic and environmental influences was assessed using bivariate twin model-fitting ($N = 3232$ twin pairs). The phenotypic correlation between internalising traits and autistic traits was $r = 0.32$ ($p < 0.001$). In univariate analyses, internalising traits and autistic traits both showed moderate heritability (52 and 53%, respectively). Cross-twin cross-trait correlations were $rMZ = 0.28$ for monozygotic twins and $rDZ = 0.16$ for dizygotic twins. In the bivariate twin analysis, an ACE Cholesky model yielded the best fit. While genetic and non-shared environmental correlations were modest ($rg = 0.22$, $re = 0.17$), a high shared environmental correlation was found ($rc = 0.77$). These results suggest that both genetic influences and shared environmental influences play a role in the association between autistic traits and internalising traits during adolescence. This work extends previous research on autistic traits and internalising traits in middle childhood (Hallett et al. 2010 Am J Psych AiA: 1–9) and presents novel information about their relationship in early adolescence.

Associations between COMT gene functional polymorphism and early-childhood internalizing symptoms: Evidence for mediation by child temperament

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Catechol-O-Methyltransferase (COMT) is a critical regulator of catecholamine levels in the brain. A growing body of literature shows that the val158met functional polymorphism of the COMT gene is linked to anxiety and depression in adolescents and adults. However, little is known about the role of this polymorphism and early-emerging internalizing symptoms. To explore this question, we investigated associations between the COMT val158met polymorphism and early childhood psychopathology symptoms in a community sample of 476 preschoolers. We also tested whether the influence of this polymorphism on child symptoms was mediated via child temperament. Symptoms of psychopathology were assessed via interviews and parent reports. The val158met polymorphism was associated with early symptoms of child anxiety and depressive symptoms such that val carriers presented with higher number of internalizing symptoms ($p < 0.01$). Mediation analysis indicated that the COMT val158met genotype was related to anxiety and depression via its influence on child inhibitory control and discomfort temperaments. In conclusion, we found evidence suggesting that functional polymorphism of the COMT gene is associated with psychopathological phenotypes in young children, and that the associations

between COMT and internalizing symptoms may be mediated by child temperament.

Whose happiness increases, and why? A longitudinal twin analysis over a decade-long interval

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We examined genetic and environmental factors contributing to stability and change of self-reported happiness over an interval of approximately 10 years. Data on subjective well-being, as measured by the negative affect on the WHO Subjective Well-being Inventory (SUBI), were collected from twins registered with the Keio Twin Project in Japan. Postal surveys were conducted twice, first in 1999/2001 and again in 2010/2011. The effective number of participants with a single response was 2031 individuals (681 MZ, 183 DZ same-sex, and 112 DZ opposite-sex pairs aged 14–33, M = 21.5). We report this data within the Time 1 period. The effective number of those with a follow-up response was 463 individuals (162 MZ, 37 DZ same-sex, and 11 DZ opposite-sex pairs), and for these individuals we report responses in Time 1 (age 14–30, M = 20.2) and Time 2 (age 23–39, M = 29.8). Going to university, getting married, or having a child did not affect the individual's later SWB as an environmental event. However, new genetic factors on SWB emerged along with going to university or getting married. Unlike previous Western findings, stability (rP = .51) of an individual's SWB was largely mediated by a common shared environmental factor (rC = 1) as well as a common genetic factor (rG = .78) in Japan. The shared environmental factor contributing to SWB had long-lasting effects and did not change in the decade between the first and second sampling periods. The factor also contributed to getting married positively and to having a child negatively. We leave further identification of the shared and nonshared environmental factors in an individual's SWB to future research.

The magnitude of genetic and environmental influences on parental and observational measures of behavioral inhibition in toddlerhood

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Behavioral inhibition is often studied in the context of how one relates to one's environment, and is a general term encompassing slow approach to novel items, shyness towards new people, and fearfulness in new situations. Individuals may develop inhibited (or the opposite, disinhibited) response styles by as early as two years, and the trait is thought to be stable across the life course. There are important methodological considerations in the study of temperament. Parental and observational measures provide both corroborative and unique data to the ascertainment of temperament and estimation of heritability, with unique variance possibly including measurement error. The present study examined the behavioral inhibition measured by parental report and observational methods in a genetically informative sample to examine the agreement between the methods and the uniqueness of each method, and estimate the magnitude of genetic and environmental influences on the common and unique variance.

Participants were twins recruited from the Colorado Longitudinal Twin Study (LTS) at the University of Colorado. Data on behavioral inhibition were recorded at 14, 20, 24, and 36 months. The present sample included 115 monozygotic (MZ) female twin pairs, 79 dizygotic (DZ) female twin pairs, 106 MZ male twin pairs, and 94 DZ male twin pairs. Parental report measures were the Toddler Temperament Scale, EAS Temperament Survey, and the Differential Emotions Scale. Observational measures included independent ratings of the participants' behavioral inhibition in multiple settings. The biometric, psychometric, and rater bias models were assessed to determine the covariance between measurement modalities. Overall, the psychometric and rater bias models fit the data well, which suggests a common phenotype was assessed by parents and observers. The covariance between parental and observational measures was found to be moderately influenced by genetic influences.

Serotonin transporter (5-HTTLPR) genotype and childhood trauma are associated with individual differences in decision making

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The factors that influence individual differences in decision making are not yet fully characterized, but convergent evidence that implicates serotonin (5-HT) system function is accumulating. Therefore, both genes and environments that influence serotonin function are good candidates for association with risky decision making. In the present study we examined associations between common polymorphisms in the serotonin transporter gene (SLC6A4), the experience of childhood trauma and decision making on the Iowa Gambling Task (IGT) in 391 (64.5% female) healthy Caucasian adults. Homozygosity for the 5-HTTLPR L allele was associated with riskier decision making in the first block of 20 trials (i.e. decision making under ambiguity). In addition, mean IGT performance was significantly worse in blocks 3-5 (i.e. decision making under risk) for those participants who reported experiencing childhood trauma. The observed pattern of mean IGT net scores suggests that those with the L/L genotype may be somewhat more sensitive to the effects of childhood trauma than S allele carriers. Our findings add to the growing evidence that genetic variation in the 5-HT system is associated with individual differences in decision making under ambiguity; and we report that the experience of childhood trauma is associated with relatively poor decision making under risk.

MAOA as a plasticity gene that moderates the association between Harsh physical discipline and externalizing symptoms in girls

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A recent theoretical perspective stipulates that particular genes may have "plasticity" alleles rather than risk alleles such that individuals with plasticity alleles are more susceptible to both positive and negative environments (Belsky et al., 2007, Current Directions in Psychological Science, 16, 300–304). We hypothesized that boys with the MAOA 3R allele would have more externalizing symptoms with harsh physical discipline and fewer symptoms with no physical discipline than those with the 4R allele. Participants were 787 twins (85% Caucasian), mean age 7.56 (.86 SD), participating in the Wisconsin Twin Project genotyped for the MAOA-VNTR (18.8% 3R, 16.7% 3/4R, 37.5% 4R, 27% Other), with mother and father reports of discipline (0 = no physical discipline, 1 = spanking with an open hand on the bottom, 2 = harsher physical discipline), and externalizing symptoms (aggression, oppositional defiant, and conduct disorder). Using multilevel regression, the MAOA x discipline x sex interaction predicted externalizing, $F(1, 561.51) = 8.19$, $p = .004$. With girls only, the MAOA x discipline interaction was significant, $F(1, 305.77) = 11.29$, $p = .001$, such that girls with the 4R alleles had the fewest symptoms in the presence of no discipline and the most symptoms in the presence of high discipline compared to girls with the 3R alleles. Both upper ($\beta = 0.24$, s.e. = 0.06, z = 4.19, $p < .0001$) and lower ($\beta = 0.20$, s.e. = 0.02, z = 8.75, $p < .0001$) bounds were significantly different. With boys, there was only a main effect of discipline on externalizing, $F(1, 382.04) = 52.88$, $p < .0001$. These findings are in contrast with previous research in boys implicating the 3R allele as a risk allele, and suggest that MAOA may function differently for girls. The current study is the first to support the differential susceptibility hypothesis for MAOA in girls.

Genetic modulators of alcohol stimulation and craving in humans

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Notable differences have been observed between craving and stimulation, and candidate genes can influence stimulation without influencing craving. Evidence shows OPRM1 as influencing stimulation, but not craving, whereas DRD4 influences craving without influencing stimulation. Two human laboratory alcohol administration studies provided an opportunity to determine the relationship between genetic modulators of alcohol-induced stimulation, craving, and alcohol consumption in alcohol dependent (AD) and non-dependent (ND) individuals.

Participants were grouped by OPRM1 status with the Asp40 variant group consisting of both heterozygous or homozygous carriers for the Asp40 variant and the Asn40 group consisting of those homozygous for the Asn40 variant. Participants were grouped by DRD4 status with the DRD4-long group, individuals with at least 1 copy of the 7 or greater repeats, and the DRD4-short group, individuals who had neither copy greater than 6 repeats.

In the AD individuals, the AA version of the OPRM1 gene was associated with a higher correlation (r = .69) between stimulation and craving than carrying the AG version (r = .21) though these correlations were not statistically different. DRD4 gene [$t(30) = .48$, $p = .64$] and OPRM1 gene [$t(28) = .78$, $p = .44$] did not predict alcohol consumed during the alcohol challenge part of the lab study. For the ND individuals, carrying the AA version of the OPMR1 gene was also associated with a higher correlation (r = .54) than the AG version (r = .20) again these correlations were not statistically different. No correlation differences were found between long or short carriers of the DRD4 gene.

The highest correlations between stimulation and craving occurred among OPRM1 AA homozygotes. G-allele carriers show greater behavioral stimulation to alcohol, but not necessarily greater urge. The AA homozygotes might be expected to show higher correlation than G-allele carriers because of divergence between the two variables.

Overlapping genetic influences on traits of autism and ADHD: Evidence from a 12-year-old community-based twin sample

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High rates of comorbidity have been reported between autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Prior research indicates that both disorders may be highly heritable, with estimates as high as 90% for ASD and 76% for ADHD. Recent research has reported moderate genetic correlations between traits of ASD and ADHD; for example, data derived from the Twins Early Development Study (TEDS) yielded genetic correlations of > .50 for these traits in middle childhood [Ronald, A. et al. (2008) J Child Psychol Psych 49 (5): 535–542]. The shared genetic overlap between ASD and ADHD has yet to be investigated longitudinally, or in early adolescence. This study aimed to explore the association between traits of ASD and ADHD in the TEDS cohort at age 12. TEDS is a community sample of twin pairs born in England and Wales between 1994 and 1996. 7,204 twin pairs provided data; parents completed the Child Autism Symptom Test and the Conners ADHD subscale. Phenotypic correlations were compared between monozygotic and dizygotic twins, and bivariate twin model-fitting was carried out using Mx. A significant phenotypic correlation was present between CAST and Conners (0.48, $p < 0.001$). Cross-trait cross-twin correlations were stronger for MZ twins (0.35) than DZ twins (0.15). An ADE model provided the best fit to the data, which estimated an additive genetic correlation of 0.54. These results in early adolescence are consistent with research with different age groups (e.g. 8-year-olds [Ronald et al., 2008), and young adults [Reiersen, A. et al. (2008) Twin Res Hum Genet 11 (6): 579–585]). These findings suggest that there are common genetic influences across traits of ASD and ADHD, which are consistent between 8- and 12-year olds in this sample. Such research has implications for molecular genetic studies and clinical evaluation of ASD and ADHD.

Classroom gains in reading fluency in first/second grade moderate etiological influences on reading comprehension in third grade

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The influence of teachers on student achievement has become as much a political issue as it is a scientific one with numerous state legislatures debating bills that tie a teacher's job to the performance of his/her students. A large body of work suggests that by the end of first grade reading achievement is largely influenced by genetic factors and yet education research showing an effect of teachers on student performance is typically conducted with samples of unrelated children that do not account for genetic effects. We recently found

that classroom gains in reading fluency (an indicator of classroom/teacher effectiveness) based on data from classmates of 806 twin pairs in first or second grade moderated unique genetic influence on reading fluency in that same grade (Taylor et al., 2010, Science, 328, 512). Genetic variance increased as classroom gains increased suggesting that in supportive classroom environments genetic differences associated with early reading fluency are able to bloom. The next question is whether early classroom/teacher effectiveness continues to influence academic performance in later school years and whether the moderation effect owes primarily to economic stratification. In this report we examined whether the effectiveness of a child's teacher for reading fluency in first or second grade moderated etiological influences on students' reading comprehension in third grade using the same sample of twins. We used census data to partial out median family income in the neighborhoods where the twins lived from the moderator. Results suggested that classroom/teacher effectiveness (classroom reading fluency gains) in first or second grade may have a distal moderation effect on genetic influences unique to reading comprehension in third grade. Results were consistent with the idea that early classroom/teacher experiences may have a lasting effect on etiological influences associated with student achievement.

Early childhood cognitive development and parental cognitive stimulation: Evidence for reciprocal gene-environment transactions

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Parenting is traditionally conceptualized as an exogenous environment that affects child development. However, children can also influence the quality of parenting that they receive. Using longitudinal data from 650 identical and fraternal twin pairs, we found that, controlling for cognitive ability at age 2 years, cognitive stimulation by parents (coded from video recorded behaviors during a dyadic task) at 2 years predicted subsequent reading ability at age 4 years. Moreover, controlling for cognitive stimulation at 2 years, children's cognitive ability at 2 years predicted the quality of stimulation received from their parents at 4 years. Genetic and environmental factors differentially contributed to these effects. Parenting influenced subsequent cognitive development through a family-level environmental pathway, whereas children's cognitive ability influenced subsequent parenting through a genetic pathway. These results suggest that genetic influences on cognitive development occur through a transactional process, in which genetic predispositions lead children to evoke cognitively stimulating experiences from their environments.

The genetic and environmental overlap between psychopathic personality and fear conditioning in 16 to 18 years old twins

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Fear conditioning is hypothesized to be the mechanism whereby individuals learn to link antisocial acts with negative consequences such as punishment or social exclusion. By failing in such emotional learning, poor fear conditioning would thus predispose an individual to antisocial behavior [2, 3]. The present study examined whether fear conditioning, as assessed by skin conductance response, is related to psychopathic personality traits, both phenotypically and genetically.

Participants were drawn from the University of Southern California (USC) Twin Project [1], a longitudinal sample including 1,185 twins born in 1995 and 1996. Psychopathic personality was assessed with the Child Psychopathy Scale [4], which was administered in interview format to the twins when they were 17–18 years old. Factor 1 corresponds to the Interpersonal + Affective sub-scale, and Factor 2 corresponds to the Behavioral + Antisocial sub-scale. The fear conditioning task consisted of presenting the subject with a neutral tone 8.0 s in duration (the conditioned stimulus, CS+) followed by a picture of an attacking dog and a 0.5 s burst of 105 db white noise, and a second neutral tone (the CS−) not followed by these negative stimuli. Five CS+ and CS− trials were presented in random order while skin conductance and heart rate responses were recorded.

Results demonstrated that fear conditioning was significantly associated with Factor 1, the Interpersonal + Affective sub-scale, but not with Factor 2, the Behavioral + Antisocial subscale. This was found for both youth self-reports and parent ratings of psychopathic personality traits. The phenotypic correlation between fear conditioning and the Interpersonal + Affective sub-scale was negative, indicating that poor fear conditioning is related to higher levels of interpersonal (e.g., manipulative, deceitful) and affective (e.g., callous, unemotional) traits. Best fitting biometric models for fear conditioning and the Interpersonal + Affective sub-scale showed that genetic influences accounted for 29% of the variance in fear conditioning, and the remaining 71% was explained by non-shared environmental influences. Genetic influences accounted for about half or less of the variance the Interpersonal + Affective sub-scale, with the remaining variance being explained by non-shared environmental influences. Genetic correlations between fear conditioning and the Interpersonal + Affective sub-scale were moderate and non-significant. Lack of significant genetic overlap may be due to low power.

The heritability of the skin conductance orienting response: A longitudinal twin study

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The orienting response is a widely used experimental paradigm that reflects the association between electrodermal activity and psychological processes. The present study examined the genetic and environmental etiology of skin conductance orienting response (SCOR) magnitude in a sample of twins assessed at ages 9–10, 11–13 and 14–16 years. Structural equation modeling within each wave showed that genetic influences explained 56, 83, and 48% of the total variance in SCOR magnitude at time point 1, 2, and 3 respectively, with the remaining variance explained by non-shared environmental factors. SCOR magnitude was moderately stable across ages, with phenotypic correlations between waves ranging from .35 to .45. A common genetic factor explained 36, 45 and 49% of the variance in SCOR magnitude across development. Age-specific genetic effects were found at ages 9–10 and 11–13 years, explaining 18 and 35% of the variance, respectively. The genetic correlations among the three waves were high, ranging from .55 to .73, indicating a substantial continuity in genetic influences from ages 9 to 16. These findings suggest that genetic factors are important influences in SCOR magnitude during adolescent development.

Both basal cortisol and CRHR1 gene variants predict fearfulness in middle childhood

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We examined the relationship between cortisol concentrations, corticotropin releasing hormone receptor 1 gene (CRHR1), and fearful behavior. The sample was comprised of 963 twin children (51.0% male) ages 7–8 years (M = 7.9, SD = .69) participating in the Wisconsin Twin Project. Children took part in in-home behavioral assessments, which were videotaped for later coding. Parents also helped youth collect saliva samples for later cortisol assays 30 min after waking, mid-afternoon, and 30 min prior to bedtime for 3 consecutive days.

The Story Telling episode, a mild analog of the Trier Social Stress Test, yielded a measure of fearful behavior—a composite of facial fear, bodily fear, and speed to display fear. We used HLM to extract predicted cortisol levels at the three average collection times ($N = 593$). We distinguished cortisol's circadian rhythm using a slopes-as-outcome approach. Collection time was centered on 7 h after waking, where we detected an inflection point in slope of cortisol concentration; a piecewise growth curve then predicted cortisol levels from Time-Before-7 h to capture the morning slope, and Time-After-7 h to capture the evening slope. We genotyped fourteen SNPs in CRHR1 ($N = 793$).

Fearful behavior was significantly negatively correlated with all cortisol measures (rs ranged −.13 to −.24) with the exception of morning cortisol level (−.03). We examined possible interactions between cortisol level, gender, and socioeconomic status (SES). There were no main effects of either gender or SES and no significant interaction with any of the basal cortisol measures. Six out of 14 SNPs were significantly associated with fearful behavior. Findings illustrate a nexus of associations among behavioral, neuroendocrine, and genetic differences that affect a domain of functioning in middle childhood.

Untreated hypertension decreases the heritability of cognition in late middle age

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Hypertension is a well-known risk factor for age-related cognitive decline, but the mechanisms underlying the effects of hypertension on cognition, particularly in midlife, are largely unknown. Heritability of midlife general cognitive ability generally ranges between 0.60 and 0.80. Developmental behavior genetic studies indicate that genetic influences on cognition over the life course are dynamic and can be modified by environmental factors. However, to our knowledge, no published study has used the twin design to quantify how hypertension may modify the importance of genetic and environmental influences on cognition. The present study examined whether hypertension moderated the genetic and environmental influences on individual differences in cognition using a large sample of middle-aged male twins. Nine cognitive domains were assessed in a sample of 1237 male twins, aged 51–60, who were divided into three blood pressure groups: non-hypertensive ($n = 548$); medicated hypertensive ($n = 424$); and unmedicated hypertensive ($n = 265$). Results revealed that the heritability was significantly lower among unmedicated hypertensives compared to medicated hypertensives and non-hypertensives for visual-spatial ability ($p = 0.013$) and episodic memory ($p = 0.004$), with a trend ($p = .067$) for abstract reasoning. However, heritability of cognitive function did not differ between non-hypertensives and medicated hypertensives. In addition, there were no significant differences in mean level cognition across any of the three hypertension groups (average effect size = 0.05, range = 0.01–0.13). These results indicate that in middle-aged men, untreated hypertension suppresses normal genetic influences on individual differences in certain domains of cognition, despite the fact that mean level differences in cognitive function have not yet developed. These analyses further suggest that antihypertensive medication may protect against or reverse this effect. This decrease in the genetic influences on individual differences in cognition may therefore be one of the mechanisms whereby hypertension causes later age-related cognitive decline.

Familial predictors of age of menarche

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Numerous studies have examined predictors of pubertal timing, but few have addressed both potential ethnic differences and genetic confounds. The current study measured pubertal timing in females, indexed by age of menarche (AOM), and examined its associations with the absence of a biological father from the household and poverty status, in early (age 0–5) and middle (age 6–9). The objectives of the study were to explore the (a) between-family associations between predictors and age of menarche, (b) potential racial/ethnic differences in these associations, and (c) within-family associations (by comparing differentially exposed cousins) between predictors and AOM.

Our sample consisted of 3,698 females of the National Longitudinal Survey of Youth 79, Young Adult, who reported AOM and race/ethnicity—21% Hispanic, 35% Black, and 44% non-Hispanic, non-Black. We found that father absence in both early (b = −0.34 years, SE = .06) and middle (b = −0.21, SE = .05) childhood, and the experience of poverty in both early (b = −.24 years, SE = .06) and middle (b = −.15, SE = .06) childhood all predicted an earlier AOM in the overall sample. The results suggest that family race/ethnicity did not moderate associations. We then found reduced between-family estimates for all variables when controlling for family background covariates, with the estimates for family poverty no longer yielding significance. Finally, we found that the within-family associations for father absence [b(early) = −.14, b(later) = −.11] and family poverty [b(early) = −.07, b(later) = −.05] were attenuated and not statistically significant when controlling for environmental and genetic confounds with cousin comparisons. The findings suggest that neither of these risks is a causal factor in accelerating pubertal timing, and that familial factors may account for associations seen in family studies.

Moderating the covariance between family member's drinking behavior

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In addition to baseline genetic predispositions toward alcohol consumption, our family members have an enormous impact on our drinking behavior. Older siblings may increase (or decrease) the availability of alcoholic beverages and afford a social environment that facilitates or inhibits consumption. Accordingly, covariance between the drinking behaviors of family members may change as a function of the age difference between the family members. In the various extended twin designs that we explore, this moderated covariance affects both common environmental as well as additive genetic variance. Thus, the greater the age difference between family members, the lower the covariance between each individual's drinking behavior at both genetic and environmental levels. We explore two implications of this finding. First, the fact that as age differences increase, the covariance between relatives decrease starts to explain why the covariance between parents and offspring is often lower than would be expected based on biometric theory. More specifically, while the typical explanation of this attenuated covariance is non-additive genetic effects, our results imply that different genes may be expressed at different ages, even in adults (Eaves et al., 1986). Second, this finding begins to vindicate the lack of findings in Candidate Gene or Genome Wide Association studies. If different genes are expressed at different ages, then the lack of significant associations between alcohol consumption and genetic variants is much more reasonable.

Reference

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The genetic etiology of cannabis use

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Cannabis is the most widely consumed illicit drug worldwide and is found to be associated with social, physical and psychological problems. It is therefore important to know what causes people to initiate cannabis use and why a subset becomes problematic users. We meta-analysed existing twin studies to estimate to what extent individual differences in cannabis use and abuse are due to genetic and environmental influences. We found that cannabis use initiation is for 48% (males) and 40% (females) due to genetic influences, while our heritability estimates for problematic use are 51% for males and 59% for females. As cannabis use phenotypes are substantially heritable it is essential to find the underlying genetic variants. Previous candidate gene studies have identified a handful of potentially important genes, but different studies have yielded inconsistent results. Therefore, we tested for replication of these identified candidate genes by running a gene-based association test in a very large ($N = 7452$) sample. We were unable to replicate any of the candidate genes. The lack of replication may point to our limited understanding of the neurobiology of cannabis involvement and also to potential publication bias and false-positive findings in previous studies. It also illustrates that to unravel the genetic etiology of cannabis use we need to use a different approach. We are now performing a large ($N > 14{,}000$) genome-wide association analysis for cannabis use, combining data from the Australian, the Netherlands, and the UK twin registries. While our sample provides considerable power we did so far not identify any genetic variants significantly contributing to cannabis use. This suggests that the biology underlying cannabis involvement is highly complex, and that our understanding of the biochemical and addictive processes governing cannabis use is nascent.

Developmental change in heritability of alcohol, nicotine, and marijuana use from age 14 to 24

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Substance use disorders are moderately to highly correlated with one another, suggesting significant common etiological processes. Much work with twin and adoption studies has been done to understand that cross-sectional shared etiology. The present work is concerned with longitudinal developmental change in substance use diagnostic symptom counts from adolescence to adulthood. We used 3767 twins from two cohorts of the community-representative Minnesota Twin Family Study measured for incident nicotine, alcohol, and marijuana dependence symptom counts at ages 11, 14, 17, 21, 24, and 29. We tested for change in comorbidity over time using a longitudinal factor model, finding that comorbidity decreased from early adolescence to adulthood. Comorbidity became increasingly stable with age, and the additive genetic variance component was responsible for the vast majority of cross-time stability. The results are consistent with the hypothesis that disinhibitory mechanisms are responsible for a portion of observed comorbidity, as these mechanisms decrease in magnitude during the same developmental interval.

Variation in the oxytocin receptor gene (OXTR) is associated with pair-bonding and social behavior

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Pair-bonding is an important part of human nature. The brain neuropeptide Oxytocin (OT) has been shown to play a central role in the regulation of pair-bonding behavior in female voles. Here, we report an association between a SNP (rs7632287) in the human oxytocin receptor gene (OXTR) and traits reflecting pair-bonding in women using two separate samples. In further analysis, the rs7632287 SNP was associated with childhood social problems, which longitudinally predicted pair-bonding behavior in one of the samples. This association was replicated in a third sample in which an association between the same SNP and social interaction deficit symptoms from the autism spectrum was detected. These results suggest an association between variation in OXTR and human pair-bonding and other social behaviors, possibly indicating that the well described influence of OT on affiliative behavior in voles could also be of importance for humans.

Parenting behaviors moderate genetic vulnerabilities to sleep problems in toddlers

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Previous research suggests that sleep problems (SP) in children are explained by genetic, shared environmental and non-shared environmental factors (Gregory et al., 2004; Van den Oord et al., 2000). However, these studies only examined the main effects of risk factors, and ignored possible G × E interactions in the etiology of SP. The present study examined whether parenting behaviors, which play an important role in the development of SP in children (Stores, 2001), moderate genetic influence on individual differences in SP.

Participants consisted of 314 same-sex twins assessed at age 2, and their parents. SP were assessed by the Sleep Problems subscale from the CBCL (Achenbach, 1991). Parental positivity and negativity were assessed using the Parent Feelings Questionnaire (PFQ; Deater-Deckard, 1996) and a semi-structured discipline interview (Deater-Deckard, 2000). Biometric moderator models (Purcell, 2002) were used to assess whether genetic and environmental influences varied across levels of parenting. Separate models were fit for parental positivity and negativity.

Analyses confirmed previous findings of genetic, shared and nonshared environmental effects on SP in children. However, parenting behaviors moderated the genetic and environmental effects on SP. Specifically, for children who experienced higher levels of parental negativity or lower levels of parental positivity, individual differences in SP were less influenced by genetic factors. When parents were more harsh or less warm, the environments played a greater role in SP. Parental negativity, but not positivity, also moderated the effects of nonshared environmental factors (i.e., the more negativity, the greater the influence of nonshared environments). This difference between positivity and negativity may be due to the different aspects of parenting associated with them. Given the fact that the genetic influences on SP are more or less important depending on the level of parental positivity/negativity, intervention on parenting behaviors may be useful in the treatment of children's SP.

Moderation by adverse environmental risk on antisocial behavior

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Previous work has established that the genetic variance related to individual differences in externalizing behavior increases in the context of each of several different environmental risk factors (Hicks, B. M., et al., 2009, Archives of General Psychiatry, 66, 640–648). Antisocial behavior is one of several aspects of externalizing, which is highly heritable. Antisocial behavior is strongly influenced by both genetic and environmental factors, and has repeatedly shown a strong shared environmental effect in adolescence (Rhee, S. H., & Waldman, I. D., 2002, Psychological Bulletin, 128, 490–529). This paper examines the moderation of the genetic and environmental variance components of adolescent antisocial behavior across risky environmental contexts at several points during the developmentally salient adolescent period. The study comes from the Minnesota Center for Twin and Family Research, and includes approximately 1200 same sex twin pairs. Participants were assessed on multiple measures of antisocial behavior at ages 11, 14, and 17 using several different informants. Adverse childhood environment was also assessed using multiple reports. We fit Cholesky models to the data and tested for heterogeneity in genetic and environmental variance components across exposure to adverse environments.

Marital quality and subjective well-being: A genetically informed investigation

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Prior research has shown that marital quality is associated with subjective well-being. It has been proposed that either marital quality influences subjective well-being or that subjective well-being influences marital quality, but less research on the possibility of common influences on both marital quality and subjective well-being has been conducted. In the current study, we estimated the magnitude of common genetic and environmental influences on the association between marital quality and subjective well-being (i.e., positive and negative affect) in a national sample of adult married twin and sibling pairs; potential gender differences in parameter estimates were also examined. Respondents completed self-report measures of positive and negative marital quality and positive and negative affect. Findings indicated that (a) positive and negative dimensions of marital quality were significantly associated with positive and negative affect, (b) parameter estimates differed significantly for males and females, (c) the covariation between marital quality and subjective well-being was higher in females than in males, (d) the covariance between marital quality and subjective well-being were primarily due to genetic influences in females; in contrast, they were evenly distributed among genetic, shared environmental, and nonshared environmental influences in males. These results support continued research on integrative models of marital functioning and subjective well-being.

Clustering of medication use in twin families from the NTR Biobank

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Data on medication use are often collected in studies of blood-derived parameters (e.g. cholesterol, glucose, cell counts), but are not always taken into account when the data are used for genetic analyses. If family members show significant clustering for medication use, the resemblance for biomarker parameters may become inflated.

The present study examines the clustering of medication use in twin families and looks at the effect of correcting for medication use, in particular on the heritability of blood-derived parameters, BMI, waist and hip circumference.

To this aim we used data from the Netherlands Twin Register (NTR) biobank (Willemsen et al., 2010), which includes information on 9530 individuals. During a home visit, participants were asked what medication they used and to provide blood and urine samples. Biomarker data include cholesterol profile, glucose metabolism, haematology and inflammation as determined in fasting blood samples.

Medication use was reported by 34.5% of the study population. Of the women, 22.9% uses oral contraceptives. Familial clustering of medication use was observed, with twin correlations indicating a heritable component underlying the use of medication. Medication use affected the level of nearly all parameters and influenced twin correlations of these parameters, such that heritability estimates were lower when no correction for medication use was performed.

Adolescent peer choice and cigarette smoking: Evidence of active gene-environment correlation?

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Both peer groups and genetics have been associated with adolescent smoking behavior. Recently, Loehlin (2010) reported that twin differences in alcohol use were associated with differences in the number of common friends. Twins with more friends in common were more similar in drinking. Furthermore, this correlation was higher for fraternal twins than for identical twins and was more pronounced for females than for males. Using the same sample as Loehlin (the National Merit twins), we replicated all of these findings for cigarette smoking. We posit four mechanisms for the peer-group relation: passive assortment, violation of the equal environments assumption, homophily, and peer influence. The pattern of results is most consistent with homophily. If peer influence occurs in the presence of homophily, then active genotype-environment correlation will be induced.

Reference

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Genetic markers of latent externalizing posttraumatic psychopathology

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This study used a candidate gene approach to evaluate the relationship between SNPs on the DAT1 and MAOA genes and externalizing psychopathology symptoms in a sample of 526 trauma-exposed veterans and their partners. The sample was comprised of 335 men and 191 women; the majority of the sample (82%) self-identified as White. Participants were assessed for an array of psychological disorders using structured clinical interviews and lifetime severity ratings on the psychiatric disorders were submitted to a confirmatory factor analysis to develop a three-factor model reflecting the latent externalizing, fear, and anxious-misery spectra. This measurement model fit the data well (chi-square = 32.96, df = 31, $p = .37$, RMSEA = .01, SRMR = .03, CFI = 1.0, TLI = 1.0) and was used in subsequent structural equation models evaluating 6 SNPs on DAT1 and 3 SNPs on MAOA genes as predictors of latent externalizing psychopathology. Preliminary quality control analyses were conducted in PLINK, as were regression analyses evaluating the association between the SNPs and dimensional symptom severity scores on each individual disorder. A series of follow-up structural equation models revealed that one SNP on the DAT1 gene (rs464528) showed significant association with latent externalizing, after controlling for race and sex. Specifically, the AA genotype on rs464528 was associated with a .99 standard score increase on latent externalizing ($p < .001$) relative to the AG and GG genotypes. These results were replicated for rs464528 when evaluated in the Caucasian subsample. Results suggest a role for DAT1 in the development of posttraumatic externalizing psychopathology and highlight the utility of examining a latent phenotype in genetic association studies.

Coding variations in the melanopsin gene predict sleep timing and seasonality

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Janine Flory
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The melanopsin gene (OPN4) has been reported to increase risk of seasonal affective disorder (SAD) in some individuals. It is possible that depression is at least partly caused by individual differences in the entrainment of the circadian clock, which may be influenced by variations in genes mediating non-visual light input such as melanopsin. We hypothesized that melanopsin gene variations increase the risk for Major Depressive Disorder (MDD) by causing abnormalities in non-visual light input. We tested associations between OPN4 polymorphisms and depression, self-reported sleep variables, and seasonality, while controlling for confounding factors. Community residents of European ancestry (age 30–54 years) from the Adult Health and Behavior Project (AHAB) registry were genotyped for OPN4 gene polymorphisms using fluorescence polarization. Participants ($N = 270$), completed the Pittsburgh Sleep Quality Index (PSQI), and were assessed for seasonality as well as Axis I diagnoses. The P10L polymorphism was associated with earlier time of awakening ($p = 0.009$) and shorter sleep duration ($p = 0.019$). The non-coding SNP rs2014084 was associated with higher seasonality ($p = 0.021$), as well as the likelihood of having both high seasonality and a diagnosis of depression ($p = 0.039$). These results indicate that OPN4 variations may influence seasonality and individual differences in sleep timing. It is possible that P10L is one of multiple genes contributing to the light sensitivity vulnerability factor. Given the role of melanopsin containing ganglion cells in conveying light information to the circadian clock for photoentrainment, it may be that melanopsin gene variations alter the sensitivity of these cells and the resultant entrainment of biological rhythms. A better understanding of the role of melanopsin in mediating non-visual light responses may improve our understanding of a broad range of behavioral responses to light (i.e., circadian, sleep, mood) as well as the biology of seasonal affective disorder.

On the likelihood ratio tests in bivariate ACDE models

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The ACE and ADE models have been heavily exploited in twin studies to identify the genetic and environmental components in phenotypes. However, the validity of the likelihood ratio test (LRT) of the existence of a variance component, a key step in the use of such models, has been doubted (e.g. Cary, 2005 and Visscher, 2006) because

the true value of the parameters lie on the boundary of the parameter space of the alternative model for such tests, violating a regularity condition required for a LRT. Our current work as presented in this paper resolves the issue of LRTs in bivariate ACDE models by exploiting the theoretical frameworks of inequality constrained LRTs based on approximating cones (Chernoff, 1954; Shapiro, 1985, 1988; Self and Liang, 1987; and Silvapulle and Sen, 2005). Our derivation shows that the asymptotic sampling distribution of the test statistic for testing a single component in the bivariate ACE or ADE model is a mixture of chi-square distributions of degrees of freedom (dfs) ranging from 0 to 3, and that for testing both the A and C (or D) components is one of dfs ranging from 0 to 6. Tests based on these mixture distributions are more powerful. The weights of the mixtures are derived and the validity of the distributions are confirmed by simulation studies. An alternative method based on Chernoff (1954) of simulating the mixture distribution is also introduced and demonstrated for attacking testing problems in multivariate ACDE models in general.

Suicidality, smoking and familial vulnerability

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Background: Smoking is a well established correlate of suicidal behavior. It is not known if this association remains after controlling for the familial contribution to the association between suicidal behavior and nicotine dependence. *Method*: Data were obtained via semi-structured interviews with 1,107 twin fathers, 1,919 offspring between ages 12–32 and 1,023 mothers. Familial vulnerability to nicotine dependence and suicidal behaviour was modeled via father and maternal self report of these behaviors. Multinomial logistic regression models were computed to estimate the association between offspring ever smoking, regular smoking, nicotine dependence and a four level offspring suicidality variable: none; ideation; ideation + plan; and ideation + plan + attempt or ideation + attempt. All models adjusted for sociodemographics, parental suicidality, nicotine dependence and conduct disorder and offspring conduct disorder and depression. Results: Ever smoking was not significantly associated with suicidality. Regular smoking was associated with ideation + plan (OR = 2.89; 95%: 1.13–7.37) and nicotine dependent smoking was associated with ideation + plan (OR = 4.17; 95% CI: 1.74–10.00) and with ideation + plan + attempt or ideation + attempt (OR = 6.72; 95% CI: 2.86–15.79). Conclusions: Smoking and nicotine dependence are correlated with suicidal behaviour. Increasing involvement in smoking was associated with increased severity of suicidality. This association remains even after controlling for familial vulnerability, parental conduct disorder and offspring conduct disorder and depression.

A MAOA gene, mother's parenting, and behavior problems: Using an MZ twin difference to detect 'pure' gene-environment interaction

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Although several studies showed the effects of measured gene-environment interaction on psychiatric and psychological outcomes, experience of environment depends on one's genetic predisposition, thus the measured gene-environment interactions observed in the literature may in fact be interactions between a measured gene and unmeasured genes. To exclude this possibility, this association study combined environmental measures as well as an MZ twin difference design to detect 'pure'14) and their mothers. Mothers completed the Child Behavior Checklist (CBCL) as well as the Parental Bonding Instrument modified for a parent-report, separately for each twin sibling. Information on children's monoamine oxidase A (MAOA) gene polymorphism (promoter variable number tandem repeat, uVNTR) was obtained from their hair roots. A series of multiple regression analyses revealed that among males, the MZ twin difference in mother's care as well as its interaction with the MAOA genotype predicted the MZ twin difference in social problems. A Sibling who received more care was less likely to have social problems ($\beta = -.39$, $p < .05$), but the effect was diminished when the sibling had at least one four-repeat allele ($\beta = .25$, $p < .05$). Similar patterns were observed for females when delinquency and aggression was predicted, as well as for other combinations of gender, parenting, and behavior problems. These results suggested that the gene–environment interactions observed in the literature are not artifact of gene–gene interactions, and in fact reflects 'pure' gene-environment interactions.

Rare copy number deletions and intelligence in schizophrenic patients and healthy controls

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The substantial heritability of human intelligence has prompted many attempts to identify specific genetic influences. Copy number variations (CNVs) represent a major type of variation. We recently reported (Yeo et al., 2011) that a higher number of rare CNV deletions and greater total length of base pairs lost through such deletions accounted for substantial phenotypic variance in intelligence. The current study evaluated the significance of rare deletion number and length in a new sample of individuals with schizophrenia and matched controls. Schizophrenics ($N = 118$) and controls ($N = 129$) were recruited from four different sites. All underwent a comprehensive neuropsychological evaluation, from which the first principle component was calculated as a measure of general ability. DNA extracted from blood samples was genotyped using the Illumina HumanOmin1-quad chip, including 1,140,419 markers. Outlier correction and principle component correction were performed to eliminate variation induced by experimental or GC content factors. The data were segmented using a circular binary segmentation algorithm and a hidden markov model algorithm (PennCNV) independently. Only CNV segments detected by both algorithms were included. A greater number of rare deletions, but not greater total length of deletions, predicted lower intellectual ability. Further, schizophrenics had more

rare deletions (as well as fewer common deletions, reduced total length of common deletions, and greater length of common duplications) than controls. In regression analyses including age, sex, race, number of rare deletions and the interaction of age with number of rare deletions, rare deletions and the age interaction were each highly significant ($p < .001$). Rare deletion number and the first PC were negatively correlated in both controls and schizophrenics.

Reference

Yeo RA Gangestad SW, Liu J et al. (2011) Rare copy number deletions predict individual variation in intelligence. PloS 6(1):e16339

Self and co-twin ratings of illicit substance use disorders

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Objective: Self and co-twin reports from male twin pairs was used to investigate the specificity of genetic and environmental risk factors for illicit substance use and substance use disorders (SUD) while correcting for random and systematic rater bias, or measurement error, creating artifactually increased comorbidity.
Method: Lifetime history of cannabis, cocaine, stimulant, hallucinogen, and sedative use, and lifetime history of cannabis, cocaine, and stimulant SUD was assessed using personal interview in 1791 male twins ascertained from a population-based twin registry. Multivariate twin analyses was used to jointly analyze self and co-twin ratings, and to estimate the relative importance of common and specific genetic, shared environmental, and unique environmental risk factors without random and systematic measurement error.
Results: Co-twin rating of illicit substance use and SUD proved to be a reliable source of information. There was a high rate of comorbidity between both use of, and SUD related to different classes of illicit substances. One common genetic, shared environmental, and unique environmental factor, respectively, and only substance specific genetic risk factors for illicit substance use were seen. For SUD, one common genetic and one common unique environmental risk factor, and substance specific shared environmental and unique environmental risk factors were identified. While comorbidity between use of different classes of illicit substances were attributed to common genetic and shared environmental factors, comorbidity between SUD was mainly explained by common genetic factors. A rater bias factor was of moderate importance in explaining artifactually increased comorbidity.
Conclusions: Risk factors for illicit substance use and SUD are to a great extent non-specific to substance class. By taking account for random and systematic measurement error, environmental exposures unique to the individual proved to be of lesser importance than what has been found in earlier studies.

Gene-environment interaction and the development of effortful control during the toddler years

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Gene–Environment interaction and the development of effortful control during the toddler years.

Lara Zappaterra, Jody M. Ganiban, Misaki Natsuaki, Jenae Neiderhiser, David Reiss, Daniel Shaw, & Leslie Leve.

Poor effortful control (EC) during toddlerhood is a risk factor for child psychopathology, but little is understood about its developmental origins. While EC is genetically influenced, environmental factors also account for variance. This study used an adoption design to estimate the relative contributions of genetic and environmental factors to children's EC at 54-months.

Participants were drawn from the Early Development and Growth Study (EGDS). EGDS is a prospective adoption study that includes 361 adoptees placed at birth, along with their adoptive parents (APs) and birth parents (BPs). Effortful control was assessed via APs' reports at 54 months. AP's parenting styles (laxness, overreactivity) were included as potential environmental predictors of effortful control, and were assessed via self-report when infants were 18- and 27-months of age. Genetic predictors included the BMs' self-reported temperament characteristics (negativity, surgency, orienting sensitivity, and effortful control). Preliminary analyses detected significant negative associations between APs' laxness and overreactivity and children's effortful control (r's −.28 to −.31, respectively). The birth mother's negativity, effortful control, surgency, and orienting sensitivity moderated these associations. High levels of BM negativity, effortful control, and orienting sensitivity enhanced negative associations between APs' overreactivity and EC. Similarly, high levels of BMs' surgency and orienting sensitivity enhanced negative associations between parental laxness and EC. However, higher levels of laxness when coupled with high BM negativity predicted higher EC. These findings identify environmental influences on EC, but also suggest that these influences interact with genetic factors in the development of EC. This reflects the importance of goodness-of-fit between parenting and children's possible genetic predispositions.

Human epigenome browser at Washington university

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Genetic studies of human behavioral disorders and addiction usually involve large amount of clinical cases and genome-wide measurements like GWAS. The resulting data is complex in nature, and presents great challenge for attempts to properly visualize such data together with the sample metadata. In the area studying human genome, same challenge arises as high-throughput DNA sequencing technologies are rapidly becoming regular laboratory procedures. To address such challenge in the latter domain, we developed Human Epigenome Browser, which can compactly represent high-throughput sequencing data as "genome heatmaps". Along with it a "clinical heatmap" is used to visualize sample metadata. We applied the Browser to the Roadmap Epigenome Project, where over 600 sequencing datasets and counting have been generated to map epigenetic changes in many human cell types. The Browser supports investigator to explore epigenomics data in great detail and flexibility. It displays data in the rich context of functional genomic features, and provides statistical functions for preliminary real-time analysis. The Browser's user interface is simple and highly interactive. It is also equipped with advanced features tailored for power users studying human genomics, including data collation, custom track, gene set view, and session. The Browser is part of the Washington University based Epigenomics Roadmap Visualization Hub (http://vizHub.wustl.edu/). We believe our tool has great application potential in human genetics studies, either as an easily accessible source of human epigenomics data, or could be adapted to visualize genome-wide human statistical genetics datasets.